STIC Search Report
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TO: Ralph J Gitomer **Location: 3d65 / 3e71** **Art Unit: 1651** **Wednesday, October 13, 2004** **Case Serial Number: 10/716975**	**From: Noble Jarrell** **Location: Biotech-Chem Library** **Rem 1B71** **Phone: 272-2556** **Noble.jarrell@uspto.gov**

Search Notes

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=> d his

     (FILE 'HOME' ENTERED AT 08:18:46 ON 13 OCT 2004)

     FILE 'HCAPLUS' ENTERED AT 08:18:53 ON 13 OCT 2004
L1             1 US20040110735/PN

     FILE 'REGISTRY' ENTERED AT 08:19:23 ON 13 OCT 2004

     FILE 'HCAPLUS' ENTERED AT 08:19:24 ON 13 OCT 2004
L2             TRA L1 1- RN :       59 TERMS

     FILE 'REGISTRY' ENTERED AT 08:19:25 ON 13 OCT 2004
L3            59 SEA L2

     FILE 'WPIX' ENTERED AT 08:19:34 ON 13 OCT 2004
L4             1 US20040110735/PN

=> b hcap
FILE 'HCAPLUS' ENTERED AT 08:20:07 ON 13 OCT 2004
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FILE COVERS 1907 - 13 Oct 2004  VOL 141 ISS 16
FILE LAST UPDATED: 12 Oct 2004  (20041012/ED)

 This file contains CAS Registry Numbers for easy and accurate
 substance identification.


=> d all l1

L1   ANSWER 1 OF 1  HCAPLUS  COPYRIGHT 2004 ACS on STN
AN   2000:133428  HCAPLUS
DN   132:185416
ED   Entered STN:  25 Feb 2000
TI   Blood-brain barrier therapeutics
IN   Ekwuribe, Nnochiri N.; Radhakrishnan, Balasingam; Price, Christopher H.;
     Anderson, Wesley R., Jr.; Ausari, Aslam M.
PA   Protein Delivery, Inc., USA
SO   PCT Int. Appl., 75 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
IC   ICM  A61K
CC   63-5 (Pharmaceuticals)
     Section cross-reference(s): 1, 34
FAN.CNT 1
     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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PI   WO 2000009073        A2    20000224    WO 1999-US18248        19990812
     WO 2000009073        A3    20000629
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             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK,
             ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG,
             CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     US 6703381           B1    20040309    US 1998-134803         19980814
     CA 2340418           AA    20000224    CA 1999-2340418        19990812
     AU 9956726           A1    20000306    AU 1999-56726          19990812
     AU 772494            B2    20040429
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EP 1105142	A2	20010613	EP 1999-943676	19990812	
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO					
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JP 2002522463	T2	20020723	JP 2000-564577	19990812	
US 2004102381	A1	20040527	US 2003-716578	20031119	
US 2004110735	A1	20040610	US 2003-716975	20031119	<--
PRAI US 1998-134803	A	19980814			
WO 1999-US18248	W	19990812			

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
WO 2000009073	ICM	A61K
US 6703381	ECLA	A61K047/48H4P
US 2004102381	ECLA	A61K047/48H4P
US 2004110735	ECLA	A61K047/48H4P <--

AB The present invention relates to amphiphilic drug-oligomer conjugates capable of traversing the blood-brain barrier and to methods of making and using such conjugates. Amphiphilic drug-oligomer conjugates comprise a therapeutic compound conjugated to an oligomer, wherein the oligomer comprises a lipophilic moiety coupled to a hydrophilic moiety. The conjugates of the invention further comprise therapeutic agents such as proteins, peptides, nucleosides, nucleotides, antiviral agents, antineoplastic agents, antibiotics, etc., and prodrugs, precursors, derivs. and intermediates thereof, chemical coupled to amphiphilic oligomers. One example conjugate prepared was Met-enkephalin with a succinimidyl triethylene glycol monohexadecyl ester derivative

ST blood brain barrier conjugate peptide oligomer

IT Enkephalins
RL: RCT (Reactant); RACT (Reactant or reagent)
(analogs; blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT Blood-brain barrier
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT Antibodies
Blood-coagulation factors
CD4 (antigen)
Hemoglobins
Hypothalamic hormones
Interferons
Opioids
Peptides, biological studies
Proteins, general, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 9004-10-8DP, Insulin, conjugates with polyoxyalkylene derivative, biological studies 259229-23-7DP, conjugates with peptides
RL: BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 57-88-5, Cholesterol, reactions 111-46-6, reactions 112-27-6, Triethylene glycol 112-82-3 623-65-4, Palmitic anhydride 4484-59-7, Triethylene glycol monohexadecyl ether 6066-82-6, Hydroxysuccinimide 13887-98-4, 3,6,9-Trioxaundecanedioic acid 58569-55-4, Met-enkephalin 74124-79-1, N,N'-Disuccinimidyl carbonate
RL: RCT (Reactant); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 5274-61-3P 31255-25-1P 62304-85-2P, Triethylene glycol monohexadecanoate 259228-98-3P 259228-99-4P 259229-23-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 4484-59-7DP, conjugates with enkephalin 5274-61-3DP, conjugates with enkephalin 62304-85-2DP, conjugates with enkephalin 259229-00-0P 259229-01-1DP, conjugates with enkephalin 259229-02-2DP, conjugates with enkephalin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

IT 50-56-6, Oxytocin, biological studies 74-79-3, Arginine, biological studies 1407-47-2, Angiotensin 9000-96-8, Arginase 9001-73-4, Papain 9001-78-9 9001-99-4, Ribonuclease 9002-07-7, Trypsin 9002-60-2, Adrenocorticotropic hormone, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9004-07-3, Chymotrypsin

9007-12-9, Calcitonin 9007-92-5, Glucagon, biological studies
9011-97-6, Cholecystokinin 9015-68-3, Asparaginase 9026-93-1,
Adenosine deaminase 9038-70-4, Somatomedin 9054-89-1, Superoxide
dismutase 11000-17-2, Vasopressin 11096-26-7, Erythropoietin
17650-98-5, Caerulein 39379-15-2, Neurotensin 51110-01-1, Somatostatin
52906-92-0, Motilin 60118-07-2, Endorphin 74913-18-1, Dynorphin
80043-53-4, Gastrin-releasing peptide 82785-45-3, Neuropeptide Y
85916-47-8, Katacalcin (human) 139639-23-9, Tissue plasminogen activator
259229-03-3 259229-04-4 259229-05-5 259229-06-6 259229-07-7
259229-08-8
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(blood-brain barrier therapeutics comprising drug-oligomer conjugates)

=> b wpix
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MOST RECENT DERWENT UPDATE: 200465 <200465/DW>
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=> d all l4

L4 ANSWER 1 OF 1 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2000-256190 [22] WPIX
DNC C2000-078134
TI Amphiphilic drug-oligomer conjugate for delivery of therapeutic agents, used to treat central nervous system disorders, or diagnostic agents across the blood brain barrier.
DC A96 B04 B05
IN ANDERSON, W R; ANSARI, A M; EKWURIBE, N N; PRICE, C H; RADHAKRISHNAN, B; AUSARI, A M; ANDERSON, W; RHADAKRISHNAN, B
PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) NOBEX CORP; (NOBE-N) NOBEX INC; (ANDE-I) ANDERSON W R; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B
CYC 83
PI WO 2000009073 A2 20000224 (200022)* EN 75 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9956726 A 20000306 (200030)
EP 1105142 A2 20010613 (200134) EN A61K031-705
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 9914280 A 20011113 (200201) A61K031-704
KR 2001072472 A 20010731 (200209) A61K047-48
CN 1323213 A 20011121 (200218) A61K031-704
JP 2002522463 W 20020723 (200263) 78 A61K047-48
MX 2001001694 A1 20020501 (200368) A61K000-00000
US 6703381 B1 20040309 (200418) A61K031-56
US 2004102381 A1 20040527 (200435) A61K038-23
US 2004110735 A1 20040610 (200438) A61K031-56 <--
AU 772494 B2 20040429 (200457) A61K031-705

ADT WO 2000009073 A2 WO 1999-US18248 19990812; AU 9956726 A AU 1999-56726 19990812; EP 1105142 A2 EP 1999-943676 19990812, WO 1999-US18248 19990812; BR 9914280 A BR 1999-14280 19990812, WO 1999-US18248 19990812; KR 2001072472 A KR 2001-701888 20010213; CN 1323213 A CN 1999-812133 19990812; JP 2002522463 W WO 1999-US18248 19990812, JP 2000-564577 19990812; MX 2001001694 A1 WO 1999-US18248 19990812, MX 2001-1694 20010213; US 6703381 B1 US 1998-134803 19980814; US 2004102381 A1 Div ex US 1998-134803 19980814, US 2003-716578 20031119; US 2004110735 A1 Div ex US 1998-134803 19980814, US 2003-716975 20031119; AU 772494 B2 AU 1999-56726 19990812

FDT AU 9956726 A Based on WO 2000009073; EP 1105142 A2 Based on WO 2000009073; BR 9914280 A Based on WO 2000009073; JP 2002522463 W Based on WO 2000009073; MX 2001001694 A1 Based on WO 2000009073; US 2004102381 A1 Div ex US 6703381; US 2004110735 A1 Div ex US 6703381; AU 772494 B2 Previous Publ. AU 9956726, Based on WO 2000009073

PRAI US 1998-134803 19980814; US 2003-716578 20031119; US 2003-716975 20031119

IC ICM A61K000-00; A61K000-00000; A61K031-56; A61K031-704; A61K031-705; A61K038-23; A61K047-48

ICS A61K038-00; A61K038-04; A61K038-11; A61K038-21; A61K038-22; A61K038-26; A61K038-27; A61K038-33; A61K038-36; A61K038-42; A61K038-46; A61K038-48; A61K039-395; A61K045-00; A61P005-02; A61P005-10; A61P005-14; A61P005-18; A61P029-00; A61P043-00; C07K014-70; C07K017-00

AB WO 200009073 A UPAB: 20000508

NOVELTY - Amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer comprising a lipophilic moiety coupled to a hydrophilic moiety, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an amphiphilic oligomer-enkephalin conjugate selected from the group consisting of DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys, cetyl Met-enkephalin-Lys, cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys, and di-palmitate-teg Met-enkephalin-Lys;

(2) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a lipophile coupled to a hydrophile by a hydrolyzable bond, the conjugate being DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys or cetyl Met-enkephalin-Lys;

(3) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a lipophile coupled to a hydrophile by a non-hydrolyzable bond, the conjugate being cholesterol Met-enkepahlin-Lys, palmitate-teg Met-enkephalin-Lys or di-palmitate-teg Met-enkephalin-Lys;

(4) a method for activating a receptor comprising bringing the receptor into contact with the novel conjugate;

(5) a method for delivering a therapeutic compound across the blood-brain barrier comprising administering the novel conjugate;

(6) a method for inducing analgesia in a subject, comprising administering the novel conjugate; and

(7) a method for altering the binding affinity of a peptide or protein to its receptor, comprising conjugating the peptide to the novel conjugate.

ACTIVITY - Cerebroprotective.

MECHANISM OF ACTION - None given.

USE - The conjugates are capable of traversing the blood-brain barrier and so delivering therapeutic agents used in the treatment of disease states associated with the central nervous system (CNS) or for delivering diagnostic agents across the blood brain barrier.

ADVANTAGE - The conjugates are stable in the bloodstream and resist degradation by the enzymes of the blood brain barrier and in the CNS. The conjugates readily cross the blood brain barrier.

Dwg.0/10

FS CPI

FA AB; DCN

MC CPI: A12-V01; B01-D02; B04-C01B; B12-K04; B14-J01

=> b home
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=> d his

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L1             1 US20040110735/PN

     FILE 'REGISTRY' ENTERED AT 08:19:23 ON 13 OCT 2004

     FILE 'HCAPLUS' ENTERED AT 08:19:24 ON 13 OCT 2004
L2               TRA L1 1- RN :       59 TERMS

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L3            59 SEA L2

     FILE 'WPIX' ENTERED AT 08:19:34 ON 13 OCT 2004
L4             1 US20040110735/PN

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                  E RECEPTORS/CT
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                  E OLIGOSACCHARIDES/CT
                  E E3+ALL
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                  E NUCLEOTIDES/CT
                  E E3+ALL

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L9            37 E3-4
                  E RADHAKRISHNAN B/AU
L10           10 E3
                  E PRICE C/AU
L11           34 E3,E10
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L12          124 E3,E20
                  E ANSARI A/AU
L13           25 E3,E7
L14           34 (PROTEIN AND DEIVERY OR NOBEX)/CS,PA
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L16           11 L15 AND L6-8
L17         3508 L5 AND L6-8
L18         1747 L5 AND (L6 OR L8) AND L7
L19           20 L18 AND L8-13
L20            9 L18 AND L14
L21            0 L20 NOT L19
L22         1727 L18 NOT L19
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L24           15 L5 AND L7 AND L8
L25           15 L24 AND L8-14
L26          758 L7 AND (LIPOPHIL? AND HYDROPHIL?)/BIX
L27           20 L5 AND L26
L28           16 L27 AND L8-14
L29            4 L27 NOT L28
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L32            6 L31 AND L8-13
L33            2 L31 AND L14
L34            0 L33 NOT L32
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                E PEPTIDES/CT
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L40          322 DRUGS+OLD,NT/CT (L) AMPHIPHIL?
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                E E3+ALL
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L42          953 POLYPEPTIDE#/CW
L43       168882 OLIGOSACCHARIDES+OLD,NT/CT
L44        57749 OLIGONUCLEOTIDES+NT/CT
L45        35325 NUCLEOTIDES+NT/CT (L) OLIGO?
L46       173581 (CARBOHYDRATE# OR SUGAR#)/CW
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                E E3+ALL
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L51           24 L50 AND L48
L52            2 L51 AND L39
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L53           61 E3-7
                E RADHAKRISHNAN B/AU
L54           55 E3,E7-8
                E PICE C/AU
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L55          123 E3,E10-11
                E PRICE CHRISTOPHER/AU
L56           36 E3,E11-12
                E ANDERSON W/AU
L57          201 E3,E48-50
                E ANDERSON WESLEY/AU
L58           35 E3,E6-8
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L59          100 E3,E13-15
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L60           11 E5
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L62            1 L51 AND L53-60
L63            1 L51 AND L61
L64            1 L62-63
L65           23 L51 NOT L64
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L69            4 L39 AND L48
L70            0 L69 AND L53-61
L71            4 L69 AND (PY<=1998 OR AY<=1998 OR PRY<=1998 OR PD<19980814 OR AD
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L73            4 L68 OR L72

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L76       593315 D1.20.230./CT
L77          806 L76 AND AMPHIPHIL?
L78          627 (D1.20.700. OR D4.635. OR D4.680.685.60. OR D4.140.)/CT AND (LI
L79           10 L75 AND L76-77 AND L78
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L80            7 E3-4
                E RADHAKRISHNAN B/AU
L81           10 E3
                E PRICE C/AU
L82          190 E3,E11-12
                E ANDERSON W/AU
L83          265 E3,E26
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L84           188 E3,E10
L85            17 (PROT? AND DELIV? OR NOBEX)/CS
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L87             0 L79 AND L85
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L90            38 L75 AND L77
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L92            17 L90 AND PY<=1998
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L94            28 L75 AND L78
L95             0 L94 AND L80-85
L96            19 L94 AND PY<=1998
                SEL AN 1-2 5-6 8 12 15
L97             7 E4-10 AND L96
                SEL AN 1-2
L98             2 E11-12 AND L97

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AN   2004-452588 [43]   WPIX
DNC  C2004-169467
TI   New modified active agent derivatives with improved bioavailability
     comprising parent drug, e.g. anticancer agent, plus fluorinated
     hydrocarbon chain and recognition or hydrophilizing moiety.
DC   A96 B04 B05 C03
IN   CONTINO, P C; DURAND, G; JASSERON, S; PERINO, S; POLIDORI, A; PUCCI, B;
     CONTINO-PEPIN, C
PA   (SALL-I) SALLES J P; (UYAV-N) UNIV AVIGNON & PAYS DU VAUCLUSE; (TSPH-N) TS
     PHARMA
CYC  107
PI   FR 2846969      A1 20040514 (200443)*      53    C07K002-00     <--
     WO 2004043993   A2 20040527 (200443)  FR         C07K002-00     <--
        RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE
            LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
         W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK
            DM DZ EC EE EG ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP
            KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG
            PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG US UZ
            VC VN YU ZA ZM ZW
ADT  FR 2846969 A1 FR 2002-14077 20021108; WO 2004043993 A2 WO 2003-FR3336
     20031107
PRAI FR 2002-14077        20021108
IC   ICM  C07K002-00
     ICS  A61K031-70; A61K031-706; A61K038-02;
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A61K047-48; A61K049-00; A61P035-00; C07H003-02; G01N033-574

AB FR 2846969 A UPAB: 20040709

NOVELTY - Modified active agent derivatives (I) containing an amino acid residue or peptide chain, a fluorinated hydrocarbon chain and a recognition or **hydrophilizing** moiety in addition to the parent active agent residue are new.

DETAILED DESCRIPTION - Modified active agent derivatives (I) containing an amino acid residue or peptide chain, a fluorinated hydrocarbon chain and a recognition or **hydrophilizing** moiety in addition to the parent active agent residue are new.

PA = active agent acting on a biological target;

x, a, b = 0 or 1;

X = peptide chain containing 1-5 amino acid residues;

AA1, AA2, AA3 = amino acids;

R = molecule recognized by the target of PA or a **hydrophilic** moiety for modifying the **hydrophilic-lipophilic** balance (HLB) value of (I);

Y1 = 4-12C fluorinated hydrocarbon chain containing a C(O), NH, OC(O)NH, S or O group allowing attachment to a terminal of the (AA3)b-(AA2)a-(AA1) chain or to the side-chain of one of the amino acids AA1-AA3;

The PA-(X)x moiety is bonded to the (AA3)b-(AA2)a-(AA1) chain via the side-chain of one of the amino acids AA1 - AA3 or to a terminal of the chain.

An INDEPENDENT CLAIM is also included for biologically active molecules containing a fragment of formula (II).

R' = monosaccharide, aminated sugar derivative, polysaccharide, polyether, polyol, peptide, natural or synthetic hormone or antibody.

ACTIVITY - Cytostatic; Antiinflammatory; Antibacterial; Analgesic; Neuroleptic; Fungicide; Antirheumatic; Antiarthritic; Antipsoriatic; Antidiabetic; Ophthalmological; Immunosuppressive; Vasotropic; Neuroprotective; Nootropic; Antiparkinsonian; Vulnerary; Dermatological.

MECHANISM OF ACTION - Antioxidant; Antiradical; Angiogenesis inhibitor.

USE - The active agent component (PA) is specifically an anticancer, anti-free radical, antiinflammatory, antiseptic, analgesic, neuroleptic or antifungal agent (all claimed). In particular various specific compounds (I) are used for treating and/or preventing cancer (e.g. where PA is Ara-C or melphalan), for detecting the presence of cancer cells (e.g. where PA comprises an Arg-Gly-Asp sequence), for treating and/or preventing disorders associated with oxidative stress and oxygenated radical species formation (e.g. where PA is N-benzylidene-tert. butylamine) or for blocking angiogenesis (e.g. where PA is thalidomide) (all claimed). Other conditions potentially treatable with (I) include rheumatoid arthritis, psoriasis, diabetic retinopathy, immunological disorders, ischemia-reperfusion syndrome, Alzheimer's disease, Parkinson's disease, lesions due to UV or ionizing radiation, melanoma and cellular aging. Cosmetic use for combating aging is also possible. The use of (II) for increasing the bioavailability of active agents is also claimed.

ADVANTAGE - (I) show improved vector/targeting properties and bioavailability compared with the parent active agents PA. They have a clearly defined structure, are easy to prepare and have controllable solubility for easy formulation.

Dwg.0/1

FS CPI

FA AB; GI; DCN

MC CPI: **A12-V01**; B02-Z; B04-B03A; **B04-C01**; **B04-C02**; **B04-C03C**; B04-D01; B04-G01; B04-J01; B06-D03; B07-D12; B10-A07; B10-A20; B10-B01A; B12-K04A1; B14-A01; B14-A02; B14-A04; B14-C01; B14-C03; B14-C09B; B14-F02D; B14-F05; B14-G01; B14-G02; B14-G03; B14-H01; B14-J01; B14-J01A3; B14-J01A4; B14-J02; B14-N03; B14-N17C; B14-R01; B14-S08; C02-Z; **C04-B03A**; **C04-C01**; **C04-C02**; **C04-C03C**; **C04-D01**; **C04-G01**; **C04-J01**; C06-D03; C07-D12; C10-A07; C10-A20; C10-B01A; C12-K04A1; C14-A01; C14-A02; C14-A04; C14-C01; C14-C03; C14-C09B; C14-F02D; C14-F05; C14-G01; C14-G02; C14-G03; C14-H01; C14-J01; C14-J01A3; C14-J01A4; C14-J02; C14-N03; C14-N17C; C14-R01; C14-S08

L74 ANSWER 2 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2004-450218 [42] WPIX

DNC C2004-168730

TI Natriuretic compound conjugate useful in the treatment of e.g. congestive heart failure, comprises natriuretic compound and at least one modifying moiety.

DC A96 B04

IN **EKWURIBE, N N**; JAMES, K D; MALKAR, N B; MILLER, M A; **RADHAKRISHNAN, B**
PA (NOBE-N) **NOBEX CORP**
CYC 105
PI WO 2004047871 A2 20040610 (200442)* EN 125 A61K047-48 <--
RW: AT BE BG BW CH CY CZ DE DK EA EE ES FI FR GB GH GM GR HU IE IT KE LS LU MC MW MZ NL OA PT RO SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NI NO NZ OM PG PH PL PT RO RU SC SD SE SG SK SL SY TJ TM TN TR TT TZ UA UG UZ VC VN YU ZA ZM ZW
ADT WO 2004047871 A2 WO 2003-US37996 20031112
PRAI US 2002-429151P 20021126
IC ICM **A61K047-48**
AB WO2004047871 A UPAB: 20040702
NOVELTY - A natriuretic compound comprises a natriuretic compound containing a natriuretic molecule NPR-A (natriuretic peptide receptor-A) binding site and at least one modifying moiety conjugation site, and at least one modifying moiety attached to the modifying moiety conjugation site.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(a) preparation of the natriuretic compound conjugate;

(b) modified pro-polynatriuretic peptide conjugate comprising: at least one natriuretic peptide unit having a modifying moiety conjugation site and an NPR-A binding site, at least one modifying moiety attached to the modifying moiety conjugation site of at least one of the natriuretic peptide units, a leader sequence and an enzymatically cleavable spacer coupling the leader spacer to a first natriuretic peptide conjugate;

(c) natriuretic peptide analog (A) comprising an amino acid sequence having at least one modifying moiety conjugation site, an NPR-A binding region and at least one substituted Lys residue, as compared to a native natriuretic peptide amino acid sequence. The substituted Lys residue is not the amino acid modifying moiety conjugation site;

(d) natriuretic peptide analog (B) comprising sequence CFGRX'1aMDRISSSSGX'2aGC;

(e) natriuretic peptide analog (C) having sequence X'1b-CFGRX'3bMDRISSSSGLGC-X'2b;

(f) natriuretic peptide analog (D) having sequence X'1c-CFGRX'3cMDRIGLGC-X'2c;

(g) natriuretic peptide analog (E) having sequence X'1d-CFGRX'3dMDRIX4GLGC-X'2d;

(h) natriuretic peptide analog (F) having sequence SPX'1eMMHX'2eSGCFGRRLDRIGSLSGLGCNVLRX'3eY3 containing a modifying moiety conjugated at the S site;

(i) a natriuretic peptide analog (G) having sequence SPZ1MVQGSG-CFGRZ2MDRISSSSX'1fX'2fX'3fC and further comprising a natriuretic peptide conjugate comprising a modifying moiety conjugated to at least one Lys residue;

(j) natriuretic peptide (H) having sequence KCFKGKNRDX'1gKX'2gQSGLX'3gC-NSFKY and further comprising a natriuretic peptide conjugate comprising a modifying moiety conjugated to at least one Lys residue;

(k) hBNP analog comprising a substitution selected from Lys14Arg or Lys14Gly; Lys27Arg or Lys27Gly; or Lys3Arg or Lys3Gly;

(l) natriuretic compound conjugate (C2) comprising natriuretic compound comprising natriuretic molecule NPR-A binding site and at least one modifying moiety conjugation site;

(m) compounds of formulae (m1)-(m6); and

(n) preparation of compounds of formulae (m1)-(m6).

X'1a = amino acid that does not comprise a conjugation site (preferably Arg);

X'2a = amino acid that comprises a modifying moiety conjugation site (preferably Lys);

X'1b = amino acid sequence containing 1-10 amino acids (preferably SPY1MVQGSS, or N-terminal tails and C-terminal segments of N-terminal tails of natriuretic peptides optionally comprising a substitution selected from Lys-to-Gly, Lys-to-Arg, Gly-to-Lys or Arg-to-Lys or an inserted Lys);

X'2b = amino acid sequence containing 1-10 amino acids (preferably Y2VLRRH, or C-terminal tails and N-terminal segments of C-terminal tails of natriuretic peptides optionally comprising a substitution selected from Lys-to-Gly, Lys-to-Arg, Gly-to-Lys or Arg-to-Lys or an inserted Lys);

X'3b = amino acid other than Lys (preferably Arg or Gly);

Y1 = modifying moiety conjugation site;

Y2 = amino acid other than Lys (preferably Arg);

X'1c = peptide containing 1-9 amino acids (preferably SPY1MVQGSG, especially SPKMVQSGS);
X'2c = peptide containing 1-6 amino acids (preferably Y2VLRRH or RVL);
X'3c = amino acid other than Lys (preferably Arg or Gly, especially Arg);
X'1d = amino acid sequence containing 1-10 amino acids (preferably a sequence native to the natriuretic peptide, especially SPY1MVQGSS);
X'2d = amino acid sequence containing 1-10 amino acids (preferably a sequence native to the natriuretic peptide, especially Y2VLRRH);
X4 = amino acid sequence containing 1-4 amino acids;
X'3d = amino acid other than Lys (preferably Arg or Gly);
Ca = alkyl;
m = 1-20;
n = 2-25;
PAG = polyalkylene glycol moiety;
n = 2-25;
Xa = a linking moiety;
Xb = O or N;
o = 1-15;
X'1e and X'2e = Lys, Arg or His;
X'3e = Arg or His;
Z1 and Z2 = Arg or an amino acid other than Lys;
X'1f = Gly, Met, Leu, Phe, Ile or their conservative substitution;
X'2f = Leu, Trp, Tyr, Phe or their conservative substitution;
X'3f = Gly or Arg or their conservative substitution;
X'1g = T, a, R, H, P, T or E;
X'2g = K, N-methyl, Arg, S, D or P;
X'3g = Arg, K, Y, F, S, Om, Har, para-amidinophenyl Ala, I or any other amino acid that has a positive charge other than Gly or Tyr;
Y3 = not defined.

ACTIVITY - Cardiant; Hypotensive.

MECHANISM OF ACTION - Natriuretic peptide receptor-A (NPR-a) agonist; Cyclic guanosyl monophosphate (cGMP) synthesis stimulator; Renin-angiotensin-aldosterone system inhibitor.

USE - The conjugates are used for the treatment of a condition involving an excess level of extracellular fluid e.g. chronic or acute congestive heart failure and hypertension (claimed).

ADVANTAGE - The modified natriuretic compound conjugates exhibit increased resistance to enzymatic degradation (preferably a protease degradation) relative to the corresponding unconjugated natriuretic compound, improved stability in the presence of plasma, proteases, liver homogenate, acidic conditions and/or basic conditions, increased circulating shelf-life, increased bioavailability and/or prolonged duration of effect, retain a therapeutically significant % of cGMP stimulating activity, such as (at least 30, preferably at least 70, especially at least 90)%, improved NPR-A receptor binding activity; improved half-life circulation, have improved ability to pass through a GI tract and enter blood stream, improved solubility in aqueous environments and organic solvents, improved ability to cross cell membranes, improved ability to traverse blood brain barrier, and improved ability to target a certain receptor, cell tissue or organ, relative to the corresponding unconjugated natriuretic compound. The modified natriuretic compound conjugates are more hydrophilic, more amphiphilic and more lipophilic than the corresponding unconjugated natriuretic compound, and is non-immunogenic. The oral administration of the natriuretic peptides due inhibition of to reduced degradation, reduces the hospital costs associated with other congestive heart failure (CHF) therapies by enabling self administration, which further expands the therapeutic use of the natriuretic peptides including administrations in early stage and acute and chronic CHF. The conjugates further lack the negative effects and risk of sudden death associated with the inotropic and digitalis drugs.

Dwg.0/5

FS CPI
FA AB; GI; DCN
MC CPI: **A12-V01**; **B04-C01C**; **B04-C01D**; **B04-C01E**; **B04-C01F**; **B04-C01G**; **B04-C03C**; B04-N02A; B04-N02B; B14-F01; B14-F02B

L74 ANSWER 3 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2003-569409 [53] WPIX
DNC C2003-153717
TI New amphiphilic ion pair complexes of pharmaceutical or cosmetic active agents with acyl-aminoacids, having good membrane penetration properties and high bioavailability.
DC B05 D21

IN CALVET, N
PA (PHYS-N) PHYSICA SARL
CYC 103
PI WO 2003055528 A2 20030710 (200353)* FR 15 A61K047-48 <--
RW: AT BE BG CH CY CZ DE DK EA EE ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SI SK SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SC SD SE SG SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
FR 2834215 A1 20030704 (200355) A61K031-195 <--
AU 2002364684 A1 20030715 (200421) A61K047-48 <--
EP 1458415 A2 20040922 (200462) FR A61K047-48 <--
R: AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI SK TR
ADT WO 2003055528 A2 WO 2002-FR4561 20021224; FR 2834215 A1 FR 2001-16936 20011227; AU 2002364684 A1 AU 2002-364684 20021224; EP 1458415 A2 EP 2002-805808 20021224, WO 2002-FR4561 20021224
FDT AU 2002364684 A1 Based on WO 2003055528; EP 1458415 A2 Based on WO 2003055528
PRAI FR 2001-16936 20011227
IC ICM **A61K031-195**; **A61K047-48**
AB WO2003055528 A UPAB: 20030820
NOVELTY - A new compound (I) for pharmaceutical or cosmetic use comprises an amphiphilic ion pair complex formed from: (A) an acyl-amino acid; and (B) a biologically active molecule useful in therapeutic or cosmetic treatment.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) dispersion system comprising a **hydrophilic** internal dispersed phase containing (I) and a **lipophilic** continuous phase; and
(2) preparation of (I).
USE - (I) are amphiphilic derivatives of the parent active agents (B), which readily cross biological membranes (thus having increased bioavailability) and/or protect (B) against excessively rapid bioconversion in the body (thus increasing the half-life in the body). (B) are specifically organic molecules, peptides with 2-20 aminoacids, nucleotides, genes, polypeptides, proteins, hormones or antigens, e.g. amoxicillin, losartan, pravastatin, diclofenac, lidocaine, vancomycin, spiramycin, neomycin, colistin, cimetidine, ranitidine, insulin, vasopressin, calcitonin, angiotensin, secretin, heparin, growth hormone, erythropoietin, parathyroid hormone or filgastrin.
ADVANTAGE - Use of (A) as the complexing agent provides amphiphilic (rather than **lipophilic**) complexes (I), which are soluble in **hydrophilic** (specifically aqueous) media and can therefore be used in aqueous solutions or in the dispersed phase of water-in-oil emulsions.
Dwg.0/0
FS CPI
FA AB; DCN
MC CPI: B02-A; B02-N; B02-P03; B02-S; B02-V; B02-V01; B04-B03B; **B04-C01B**; **B04-C02E**; B04-J03A; B04-J04A; B04-N04; B04-N06; B07-A01; B07-D09; B07-D13; B10-B02; B10-B02A; B10-B02B; B10-B02F; B10-C04A; B10-C04E; B12-M05; B14-R01; D08-B

L74 ANSWER 4 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2003-221302 [21] WPIX
DNC C2003-056080
TI Monodispersed mixture of conjugates useful in treatment of disease e.g. diabetes comprises drug coupled to oligomer containing polyalkylene glycol moiety.
DC A96 B04 D16
IN **ANSARI, A M**; **EKWURIBE, N N**; ODENBAUGH, A L; **PRICE, C H**
PA (NOBE-N) **NOBEX CORP**; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H
CYC 101
PI WO 2002098446 A1 20021212 (200321)* EN 101 A61K038-02 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
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BR 2001006401 A 20030211 (200321) A61K047-48 <--

JP 2003104913 A 20030409 (200333) 308 A61K047-48 <--
US 2003228275 A1 20031211 (200382) A61K038-00 <--
EP 1404355 A1 20040407 (200425) EN A61K038-02 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
AU 2002310289 A1 20021216 (200452) A61K038-02 <--

ADT WO 2002098446 A1 WO 2002-US17567 20020604; BR 2001006401 A BR 2001-6401 20011011; JP 2003104913 A JP 2001-317307 20011015; US 2003228275 A1 US 2001-873797 20010604; EP 1404355 A1 EP 2002-737357 20020604, WO 2002-US17567 20020604; AU 2002310289 A1 AU 2002-310289 20020604

FDT EP 1404355 A1 Based on WO 2002098446; AU 2002310289 A1 Based on WO 2002098446

PRAI US 2001-873797 20010604

IC ICM **A61K038-00**; **A61K038-02**; **A61K047-48**
ICS **A61K031-765**; **A61K038-17**; **A61K038-18**; **A61K038-19**; **A61K038-22**; **A61K038-23**; **A61K038-28**; A61K039-02; A61K039-12; A61K039-385; A61K047-34; A61P005-00; A61P043-00; **C07K001-107**; **C07K001-113**; **C07K002-00**; **C07K014-475**; **C07K014-52**; **C07K014-575**; **C07K014-585**

AB WO 200298446 A UPAB: 20030328

NOVELTY - A substantially monodispersed mixture of conjugates comprises a drug coupled to an oligomer (a) containing a polyalkylene glycol moiety (b).

DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for synthesizing a monodispersed mixture of conjugate, that involves:

(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture containing compounds of formula R2(OC2H4)q-OMs (II) to form a monodispersed mixture comprising polymers of formula R2(OC2H4)m+q-OR1 (III);

(ii) activating (III) to form a monodispersed mixture of activated polymers capable of reacting with a drug; and

(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to form a monodispersed mixture of conjugates comprising drug coupled to an oligomer containing polyethylene glycol with m+p subunits.

R1 and R2 = H or lipophilic moiety;
m, q = 1 - 25; and
X+ = positive ion.

ACTIVITY - Antidiabetic.

MECHANISM OF ACTION - None given.

USE - In the treatment of disease states e.g. insulin deficiency.

Male CF-1 mice were housed in a room. Mice were acclimated to housing conditions for 48 - 72 hours prior to the day of experiment. Prior to dosing, mice were fasted overnight and water was provided ad libitum. Mice were distributed into groups of five animals per time point and were administered a single oral dose of a PEG7-octyl-(sCT), diconjugate (Octyl Di) (test) or salmon calcitonin (sCT or Calcitonin) for comparison purposes. Oral doses were administered at 10 ml/kg in a phosphate-buffered PEG7-octyl-sCT, diconjugate formulation. The buffered formulation was prepared by adding phosphate buffer (80 mL) in a beaker. The sodium cholate was added to the phosphate buffer with stirring until dissolved. The deoxy cholate was then added and stirring was continued until dissolved. The PEG7-octyl-sCT, diconjugate, solution was added. The remaining phosphate buffer was added to achieve a final weight of 100 g. Dose-response curves were constructed. At appropriate time points, mice were ether-anesthetized, the vena cavae exteriorized, and blood samples were obtained. Blood aliquots were clotted at 22 deg. C for 1 hour, and the sera removed and pipetted into a clean receptacle. Total serum calcium was determined for each animal. Serum calcium data were plotted and pharmacokinetic parameters determined. Means and standard deviations (or standard errors) were calculated and plotted to determine effect differences among dosing groups. The % baseline calcium drop at 2 micro g/kg dose for the test was 21%. The in vitro activity of PEG7-octyl-sCT and PEG7-decyl-sCT mono- and diconjugates, the stearate-PEG6-sCT, diconjugate, and stearate-PEG8-sCT, diconjugate, appeared to have in vivo activity that was comparable with the in vivo activity observed for the PEG7-octyl-sCT and PEG7-decyl-sCT, mono- and di-conjugates. The improved in vivo activity of the stearate containing conjugates indicated that these conjugates were undergoing hydrolysis in vivo to provide an active salmon calcitonin or active salmon calcitonin-PEG conjugate.

ADVANTAGE - The mixture exhibits greater in vivo/in vitro activity than the in vivo/in vitro activity of the polydispersed mixture of drug-oligomer conjugates having same number of average molecular weight as the mixture. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by

chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugate mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having same number average molecular weight as the mixture.

Dwg.0/43

FS CPI

FA AB; GI; DCN

MC CPI: **A12-V01**; **B04-C01**; **B04-C03**; **B04-C03C**; B04-H01; B04-J01; B04-N01; B04-N02; B04-N03; B14-S04; D05-H12D

L74 ANSWER 5 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2003-210058 [20] WPIX

DNC C2003-053443

TI Monodispersed mixture of conjugates useful in the treatment of diabetes comprises an insulin drug coupled to an oligomer containing a polyethylene glycol moiety.

DC A25 A96 B04

IN **ANSARI, A M**; **EKWURIBE, N N**; ODENBAUGH, A L; **PRICE, C H**; **RADHAKRISHNAN, B**

PA (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (ODEN-I) ODENBAUGH A L; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B; (NOBE-N) **NOBEX CORP**

CYC 101

PI WO 2002098232 A1 20021212 (200320)* EN 64 A01N061-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003027748 A1 20030206 (200320) A61K038-28 <--
BR 2001006851 A 20030408 (200329) A61K038-28 <--
JP 2003113113 A 20030418 (200335) 182 A61K038-28 <--
EP 1404178 A1 20040407 (200425) EN A01N061-00
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2004004692 A 20040113 (200434) A61K038-28 <--
AU 2002310291 A1 20021216 (200452) A01N061-00

ADT WO 2002098232 A1 WO 2002-US17574 20020604; US 2003027748 A1 US 2001-873899 20010604; BR 2001006851 A BR 2001-6851 20011011; JP 2003113113 A JP 2001-316998 20011015; EP 1404178 A1 EP 2002-737359 20020604, WO 2002-US17574 20020604; KR 2004004692 A KR 2003-715910 20031204; AU 2002310291 A1 AU 2002-310291 20020604

FDT EP 1404178 A1 Based on WO 2002098232; AU 2002310291 A1 Based on WO 2002098232

PRAI US 2001-873899 20010604

IC ICM A01N061-00; **A61K038-28**
ICS A01N037-18; **A61K031-00**; **A61K038-00**; A61K047-34; **A61K047-48**; A61P003-10; A61P005-50; **C07K014-62**

AB WO 200298232 A UPAB: 20030324

NOVELTY - A substantially monodispersed mixture of conjugates comprising an insulin drug coupled to an oligomer (a) containing a polyethylene glycol moiety (b), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a substantially monodispersed mixture of conjugates (A') comprising human insulin covalently coupled at Lys-B29 of the human insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol having at least 7 polyethylene glycol subunits; and

(2) a method of synthesizing a monodispersed mixture of conjugates comprising:

(i) reacting a monodispersed mixture containing compounds of formula R1(OC2H4)m-O-X+ (I) with a substantially monodispersed mixture comprising compound of formula R2(OC2H4)n1-OMs (II) to provide a monodispersed mixture comprising polymers of formula R2(OC2H4)m+n1-OR1 (III);

(ii) activating (III) to provide a monodispersed mixture of activated polymers capable of reacting with insulin drug; and

(iii) reacting the monodispersed mixture of activated polymers with a monodispersed mixture of drugs to provide a monodispersed mixture of conjugates comprising insulin drug coupled to an oligomer containing polyethylene glycol with m+n1 subunits.

R, R2 = H or lipophilic moiety;

m, n1 = 1-25;

X+ = positive ion.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - None given.
USE - The mixture is used in the treatment of insulin deficiency in a subject (claimed).
ADVANTAGE - The mixture exhibits greater in vivo/vitro activity than the in vivo/vitro activity of the polydispersed mixture of insulin drug-oligomer conjugates having same number of average molecular weight as the mixture respectively. The mixture has increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugate mixture having same number average molecular weight as the mixture. The mixture has inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having same number average molecular weight as the mixture.
Dwg.0/21
FS CPI
FA AB; GI; DCN
MC CPI: **A12-V01**; **B04-C03C**; B04-J03A; B14-S04

L74 ANSWER 6 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2003-183863 [18] WPIX
DNC C2003-048349
TI Insulin composition for pulmonary administration in the treatment of diabetes comprises a conjugate of insulin covalently coupled to a non-naturally occurring **hydrophilic** polymer.
DC A96 B04
IN BUECHE, B; HARRIS, J M; KUO, M; LEACH, C; PATTON, J S; PERKINS, K; KUO, M K
PA (NEKT-N) NEKTAR THERAPEUTICS; (NEKT-N) NEKTAR THERAPEUTICS AL CORP; (BUEC-I) BUECHE B; (HARR-I) HARRIS J M; (KUOM-I) KUO M; (LEAC-I) LEACH C; (PATT-I) PATTON J S; (PERK-I) PERKINS K; (INHA-N) INHALE THERAPEUTIC SYSTEMS INC; (SHEA-N) SHEARWATER CORP
CYC 101
PI WO 2002094200 A2 20021128 (200318)* EN 43 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003118510 A1 20030626 (200343) A61L009-04
US 2003216542 A1 20031120 (200377) C07K005-00 <--
NO 2003005157 A 20040112 (200412) A61L000-00
EP 1395294 A2 20040310 (200418) EN A61L009-04
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
KR 2003097876 A 20031231 (200427) A61K047-48 <--
SK 2003001553 A3 20040608 (200441) A61K009-24
AU 2002303869 A1 20021203 (200452) A61K000-00
BR 2002009896 A 20040817 (200457) A61L009-04
CZ 2003003182 A3 20040915 (200462) A61L009-04
ADT WO 2002094200 A2 WO 2002-US16464 20020521; US 2003118510 A1 Provisional US 2001-292423P 20010521, US 2002-154057 20020521; US 2003216542 A1 Provisional US 2001-292423P 20010521, Cont of US 2002-154057 20020521, US 2003-405190 20030401; NO 2003005157 A WO 2002-US16464 20020521, NO 2003-5157 20031120; EP 1395294 A2 EP 2002-731931 20020521, WO 2002-US16464 20020521; KR 2003097876 A KR 2003-714954 20031117; SK 2003001553 A3 WO 2002-US16464 20020521, SK 2003-1553 20020521; AU 2002303869 A1 AU 2002-303869 20020521; BR 2002009896 A BR 2002-9896 20020521, WO 2002-US16464 20020521; CZ 2003003182 A3 WO 2002-US16464 20020521, CZ 2003-3182 20020521
FDT EP 1395294 A2 Based on WO 2002094200; SK 2003001553 A3 Based on WO 2002094200; AU 2002303869 A1 Based on WO 2002094200; BR 2002009896 A Based on WO 2002094200; CZ 2003003182 A3 Based on WO 2002094200
PRAI US 2001-292423P 20010521; US 2002-154057 20020521; US 2003-405190 20030401
IC ICM A61K000-00; A61K009-24; **A61K047-48**; A61L000-00; A61L009-04; **C07K005-00**
ICS **A61K038-00**; **A61K038-16**; **A61K038-28**
AB WO 200294200 A UPAB: 20030317
NOVELTY - An insulin composition for pulmonary administration comprises a conjugate of insulin (A) covalently coupled to at least one molecule of a non-naturally occurring **hydrophilic** polymer (B) and an

excipient.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:
(1) Method (M1) for delivering (A) involving administering aerosolized insulin composition by inhalation for deposition in and absorption from the lungs of the subject; and
(2) Method (M2) for providing non-immunogenic insulin composition to the lungs involving covalently coupling (A) to at least one (B), and administering the composition to the lungs by inhalation. The insulin passes through the lung and enters into the blood circulation.
ACTIVITY - Antidiabetic.
MECHANISM OF ACTION - None given.
USE - For pulmonary delivery of insulin to the lungs of mammalian subject (claimed) in the treatment of diabetes mellitus, type I and type II diabetes.
ADVANTAGE - The composition has an absolute pulmonary bioavailability greater than (preferably greater than 15%, especially greater than 30%, particularly at least twice) that of native insulin. The composition has Tmax of at least three times (preferably at least five times) that of native insulin. The composition elevates the blood level of insulin for at least 8 (preferably at least 10, especially at least 12) hours post administration. The composition increases the serum level of insulin at least 2 times greater than the basal level within 1 hour post administration.
Dwg.0/14

FS CPI
FA AB; DCN
MC CPI: A05-H01B; A10-E01; **A12-V01**; **B04-C03C**; B04-J03A; B12-M01A; B12-M01B; B14-S04

L74 ANSWER 7 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2003-046722 [04] WPIX
DNC C2003-011825
TI Treatment of diabetes mellitus using an insulin-polypeptide derivative.
DC A96 B04
IN **EKWURIBE, N N**; FILBEY, J A; **PRICE, C H**; STILL, J G; **ANSARI, A M**; ODENBAUGH, A L; **RADHAKRISHNAN, B**
PA (EKWU-I) EKWURIBE N N; (FILB-I) FILBEY J A; (PRIC-I) PRICE C H; (STIL-I) STILL J G; (NOBE-N) **NOBEX CORP**
CYC 101
PI WO 2002065985 A2 20020829 (200304)* EN 114 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW
US 2003050228 A1 20030313 (200321) A61K038-28 <--
AU 2002244020 A1 20020904 (200427) A61K000-00
EP 1409006 A2 20040421 (200427) EN A61K038-28 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
JP 2004527487 W 20040909 (200459) 187 A61K038-28 <--
KR 2004043113 A 20040522 (200460) A61K038-28 <--
ADT WO 2002065985 A2 WO 2002-US4440 20020214; US 2003050228 A1 Provisional US 2001-269198P 20010215, US 2002-75097 20020213; AU 2002244020 A1 AU 2002-244020 20020214; EP 1409006 A2 EP 2002-709541 20020214, WO 2002-US4440 20020214; JP 2004527487 W JP 2002-565546 20020214, WO 2002-US4440 20020214; KR 2004043113 A KR 2003-710645 20030813
FDT AU 2002244020 A1 Based on WO 2002065985; EP 1409006 A2 Based on WO 2002065985; JP 2004527487 W Based on WO 2002065985
PRAI US 2002-347713P 20020111; US 2001-269198P 20010215; US 2002-75097 20020213
IC ICM A61K000-00; **A61K038-28**
ICS **A61K047-48**; A61P003-10; **C07K014-62**
AB WO 200265985 A UPAB: 20030117
NOVELTY - Treatment of diabetes mellitus comprises orally administering an insulin-polypeptide derivative (I) to a patient within one hour of ingestion of a meal so that it provides an insulin drug concentration in portal vein blood between 10 and 1,000 U/ml within about 60 minutes of administration .
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is included for the use of (I) in the manufacture of an oral medicament for the treatment of diabetes mellitus.
ACTIVITY - Antidiabetic.
Pancreactomized and normal, fasted dogs were orally administered with

a polydispersed mixture of insulin polypeptide -NH-C(O)-(CH2)5(OC2H4)7OCH3 (1 mg/kg). At the given dosage of the insulin, all the dogs required glucose rescue, due to marked symptomatic hypoglycemia.

MECHANISM OF ACTION - None given.

USE - In the treatment of diabetes mellitus (claimed).

ADVANTAGE - (I) provides an insulin drug concentration in portal vein blood from about 10 - 1000 U/ml in about 60 (preferably 30) minutes of administration; provides maximum insulin drug concentration in peripheral blood in about 60 minutes; stabilizes peripheral glucose concentration to plus or minus 50% of average peripheral glucose concentration in 30 - 60 minutes; clears the bloodstream of a patient in about 4 hours; and reduces hepatic glucose production in a patient by at least 25% in about 90 minutes. At least 25% of post-prandial glucose resulting from ingestion of a meal by the patient is hepatically absorbed in about 120 minutes after injection of the meal (all claimed).

Dwg.1a/20

FS CPI

FA AB; GI; DCN

MC CPI: **A12-V01**; **B04-C03C**; B04-J03A; B14-S04

L74 ANSWER 8 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2002-657431 [70] WPIX

DNC C2002-184421

TI New amide-linked mono, di and tri-saccharide-lipoamino acid complex useful in drug delivery.

DC B07 C07

IN FALCONER, R; TOTH, I; DE CRUZ, S E; MCGEARY, R P; ROSS, B P

PA (ALCH-N) ALCHEMIA PTY LTD; (DCRU-I) DE CRUZ S E; (FALC-I) FALCONER R; (MCGE-I) MCGEARY R P; (ROSS-I) ROSS B P; (TOTH-I) TOTH I

CYC 100

PI WO 2002053572 A1 20020711 (200270)* EN 66 C07H015-04

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW

AU 2002216843 A1 20020716 (200427) C07H015-04

US 2004176281 A1 20040909 (200459) A61K038-16 <--

ADT WO 2002053572 A1 WO 2002-AU5 20020103; AU 2002216843 A1 AU 2002-216843 20020103; US 2004176281 A1 CIP of WO 2002-AU5 20020103, US 2003-676436 20030630

FDT AU 2002216843 A1 Based on WO 2002053572

PRAI GB 2001-115 20010104

IC ICM **A61K038-16**; C07H015-04

ICS **A61K031-715**; **A61K038-14**; A61K047-26; A61K047-36; **A61K047-48**; C07H015-12; **C07K009-00**

AB WO 200253572 A UPAB: 20021031

NOVELTY - Amide-linked mono, di and tri-saccharide-lipoamino acid complex (I) is new.

DETAILED DESCRIPTION - Amide-linked mono, di and tri-saccharide-lipoamino acid complex of formula r(D(nz))pQ (I) is new.

Q = carrier compound of formula ((Wq-S-X-L)(my));

D = therapeutically useful molecule;

r = 0 o not more than 0;

p = not more than 1;

n, m = not more than 1 and represent overall magnitude of the charge on the molecule;

z, y = positive or negative charges;

X = covalent bond or is a linker group selected from 2-14 atom spacers;

S = mono- or oligosaccharide;

L = lipidic moiety

W = 3-10C (hetero)alkyl (optionally branched) and is substituted with at least one functional group which is charged or carries a charge under physiological conditions; and

q = 0 when W is absent or ranges from 3 to the number of hydroxyls available for substitution on the mono- or oligosaccharide.

INDEPENDENT CLAIMS are also included for the following:

(1) preparation of (I);

(2) delivering a therapeutically useful molecule comprising administering (I).

ACTIVITY - Cytostatic; Nootropic; Neuroprotective; Cardiant; Hypotensive; Antiarteriosclerotic.

MECHANISM OF ACTION - None given in the source material.

USE - For treating or preventing a pathological condition and in the delivery of a therapeutically useful molecule (claimed), for treating neoplasm, cancers (e.g. cancers of breast, lung etc), fibrotic disorder, disorder of the central nervous system (e.g. Alzheimer's disease), dementia, memory loss, motor neuron disease, disorder of cardiovascular system (e.g. cardiac hypertrophy, congestive heart failure, hypertension, hormonal imbalance, atherosclerosis), and disorders of development and growth (including disorders of glucose and fat metabolism).

ADVANTAGE - The complex is as an ionic delivery system, in which the drug molecule and the delivery system form an ionic complex. The complex does not require the chemical conjugation of the drug molecule and therefore does not alter the pharmaceutical properties of the drug molecule. The complex can also be used to target either passive or active transport mechanisms and is readily optimized for **hydrophilic** drug molecules, peptides and proteins and offers significant benefits in terms of regulatory approval.

Dwg.0/0

FS CPI

FA AB; DCN

MC CPI: **B04-C02V**; B14-F01; B14-F02; B14-H01B; B14-J01; B14-K01; B14-S04; **C04-C02V**; C14-F01; C14-F02; C14-H01B; C14-J01; C14-K01; C14-S04

L74 ANSWER 9 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2002-519168 [55] WPIX

DNC C2002-146835

TI New synthetic regulatory compound useful for combating infections by pathogens comprises non-natural nucleic binder, a regulatory moiety and a linker.

DC B03 C02 D16

IN **ANSARI, A**; DERVAN, P; MAPP, A; PTASHNE, M

PA (CALY) CALIFORNIA INST OF TECHNOLOGY; (SLOK) SLOAN KETTERING INST CANCER RES

CYC 88

PI WO 2002034295 A1 20020502 (200255)* EN 103 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZA ZW
AU 2001013481 A 20020506 (200257) A61K047-48 <--

ADT WO 2002034295 A1 WO 2000-US29617 20001027; AU 2001013481 A WO 2000-US29617 20001027, AU 2001-13481 20001027

FDT AU 2001013481 A Based on WO 2002034295

PRAI WO 2000-US29617 20001027

IC ICM **A61K047-48**
ICS A61K049-00

AB WO 200234295 A UPAB: 20020829

NOVELTY - A synthetic regulatory compound (I) or its salt comprises a non-natural nucleic acid binding moiety (a), a regulatory moiety (b) and a linker (c) connecting (b) to (c).

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:

(1) a cell in vitro or in vivo comprising (I);

(2) a complex comprising (I) complexed with a double-stranded DNA;

(3) forming the complex involving exposing a composition (preferably a cell) containing a double-stranded DNA containing target sequence to (I);

(4) regulating transcription of a regulatable gene in vitro or in vivo involving exposing a double-stranded DNA encoding the regulatable gene to (I) capable of regulating its transcription under transcription condition; and

(5) screening (I) in vitro or in vivo involving exposing the double-stranded DNA encoding the regulatable gene (preferably marker gene) to several test compounds and determining whether the test compound regulates expression of the regulatable gene.

ACTIVITY - Fungicide; Anti-bacterial; Virucide; Cytostatic; Vasotropic; Antipsoriatic; Antiarteriosclerotic; Hypotensive; Dermatological; Antidepressant; Antiinflammatory; Antirheumatic; Antiarthritic; Hepatotropic; Antiallergic; Antiulcer; Cardiovascular-General; Immunosuppressive; Neuroprotective; Antidiabetic; Thyromimetic.

No supporting data provided.

MECHANISM OF ACTION - Gene expression inhibitor; Gene activator; Modulator; Expression of specific gene regulator.

The synthetic regulatory compounds used employed polyamide molecules

as non-natural nucleic acid binding moieties. The compounds were tested a cell line of SKOV (a cisplatin resistant human ovarian cancer cell line). The compounds were also tested for their ability to activate a transiently transfected reporter gene the expression of which could be up-regulated by activation of a promoter functionally associated with one DR5 target site. The reporter gene carried by the cells comprised a minimal HSV TK promoter driving the expression of a luciferase gene. Promoter activity was regulated by a consensus DR5 site approximately 50 bp upstream of the TK promoter. The DR5 site comprised a direct repeat of two consensus hexameric sequences separated by five nucleotides, the identity of which was irrelevant. One of the consensus hexameric nucleotide sequences in the DR5 site was 5'-AGGTCA-3', which also corresponded to an estrogen receptor half site. The polyamide moieties of the synthetic regulatory compounds used in this experiment targeted the nucleotide sequence 5'-WGGWCA-3', and were fused via a PEG linker at the C-terminal tail to either the L- or the D- form of a VP2 activating region (Amv154 and Amv155 respectively). Prior to testing these two conjugates on reporter cells, these compounds were tested for their ability to activate transcription in standard cell-free yeast system that comprised a reporter construct having three tandem 5'-AGGTCA-3' sites located 40 bp upstream of the AdML TATA:G-less cassette. The in vitro transcription experiments were performed. The Amv151 polyamide alone did not stimulate transcription over basal conditions. The synthetic regulatory compound Amv154 (PA-1L-VP2) activated transcription about 12 fold, and Amv155 (PA-1L-D-VP2) activated transcription about ten-fold in the in vitro assays. The observed levels of activation were consistent with the fact that only three half sites, rather than three complete palindromes, were used in the reporter construct employed in the in vitro transcription assays. The cells used for the cell permeability and cell-based reporter assays were passaged twice and then grown overnight in 6-well plates to sub-confluency in CO2 incubators. Two micrograms of DR5-Luc DNA and 0.5 micrograms of CMV- beta gal were transfected in each of the wells. One well on each plate contained no reporter construct, and one contained a strong CMV promoter driving the Luc reporter gene to check for transfection efficiency. SKOV cells were transfected using DOTAP (a cationic lipid transfection system). After DNA addition, the cells were incubated for 12 hours and then washed with fresh DMEM media containing 10% charcoal-stripped Fetal Bovine Serum. Cells were then allowed to recover for 12 hours in 2 ml of DMEM+15% FBS (stripped). After washing out this media, cells were supplied with 1 ml of DMEM+10% FBS (stripped) containing AMv151, Amv154, or Amv155 at 1 mu M concentrations. Luciferase activity was measured using standard luminomitor techniques. For reporter of cells alone, conjugate (none given), the luciferase activity was 464. For reporter of CMV-Luc and conjugate (none given), the luciferase activity was 859304. For reporter of DR5-Luc without any conjugate, the luciferase activity was 828117. For reporter of DR5-Luc with conjugate of AMv151/AMv154/Amv155, the luciferase activity was 400439/570395/703533 and the normalized activation was 1/1.425/1.75 respectively.

USE - In composition such as liquid composition or dry composition; and in a cell (e.g. animal cell, plant cell, bovine, canine, equine, feline, murine, ovine, porcine, primate cell or human cell) also in regulating transcription of a regulatable gene (claimed). For combating infections by pathogens including protozoa, virus; for treating eukaryotic organisms such as plants such as agricultural crop and animals such as bovines, canine, equine, feline, ovine etc; to modulate physiological processes in vivo. In the treatment of cancer, restenosis, psoriasis, lymphopoiesis, atherosclerosis, pulmonary fibrosis, primary pulmonary hypertension, neurofibromatosis, acoustic neuroma, tuberous sclerosis, keloid, fibrocystic breast, polycystic ovary and kidney, scleroderma, inflammatory diseases such as rheumatoid arthritis, ankylosing spondilitis, myelodysplasia, cirrhosis, esophageal stricture, sclerosing cholangitis, retroperitoneal fibrosis, skin graft rejection, allergic response, psychosis, sleep regulation, immune response, mucosal ulceration, withdrawal symptoms associated with termination of substance use, pathogenesis of liver injury, cardiovascular processes, neuronal processes, autoimmune diseases; for down-regulating the gene coding for the RNA and protein components of telomerase; and in agricultural and medicinal applications.

ADVANTAGE - (I) is cell permeable. (I) exhibits good anti-fungal and anti-bacterial (Gram-positive, Gram-negative, aerobic and anaerobic) properties.

Dwg.0/17

FS CPI

FA AB; DCN

MC CPI: B04-E01; B04-F01; B11-C08; B12-K04; B14-A02; B14-C09B; B14-F01; B14-F02; B14-F02B; B14-F07; B14-G02C; B14-H01; B14-J01; B14-K01;

B14-N10; B14-N12; B14-N17C; B14-S04; B14-S06; **C04-E01**; **C04-F01**; C11-C08; C12-K04; C14-A02; C14-C09B; C14-F01; C14-F02; C14-F02B; C14-F07; C14-G02C; C14-H01; C14-J01; C14-K01; C14-N10; C14-N12; C14-N17C; C14-S04; C14-S06; D05-H09

L74 ANSWER 10 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2002-268849 [31] WPIX
CR 1999-105499 [09]; 2002-280618 [32]; 2003-669500 [63]
DNN N2002-209278 DNC C2002-079681
TI Method for treating vaginal or uterine fungal, bacterial, viral and parasitic infections comprises intravaginal or transvaginal administration of an antifungal, parasiticidal, antibacterial or antiviral agent.
DC A96 B05 C03 D22 F07 P32 P34
IN DAUGUSTINE, M A; HARRISON, D C; LIU, J H; D'AUGUSTINE, M A
PA (UMDU-N) UMD INC
CYC 95
PI WO 2002003896 A1 20020117 (200231)* EN 49 A61F006-06
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2001081287 A 20020121 (200234) A61F006-06
EP 1301150 A1 20030416 (200328) EN A61F006-06
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR
BR 2001012571 A 20030527 (200344) A61F006-06
JP 2004508296 W 20040318 (200420) 73 A61K047-48 <--
MX 2002012819 A1 20030901 (200465) A61F013-00
ADT WO 2002003896 A1 WO 2001-US41128 20010625; AU 2001081287 A AU 2001-81287 20010625; EP 1301150 A1 EP 2001-959766 20010625, WO 2001-US41128 20010625; BR 2001012571 A BR 2001-12571 20010625, WO 2001-US41128 20010625; JP 2004508296 W WO 2001-US41128 20010625, JP 2002-508356 20010625; MX 2002012819 A1 WO 2001-US41128 20010625, MX 2002-12819 20021219
FDT AU 2001081287 A Based on WO 2002003896; EP 1301150 A1 Based on WO 2002003896; BR 2001012571 A Based on WO 2002003896; JP 2004508296 W Based on WO 2002003896; MX 2002012819 A1 Based on WO 2002003896
PRAI US 2000-613441 20000711
IC ICM A61F006-06; A61F013-00; **A61K047-48**
ICS A61F013-02; A61F013-20; A61K009-02; A61K009-06; A61K009-08; A61K009-10; A61K009-12; A61K009-14; A61K009-20; **A61K031-4164**; **A61K031-4174**; **A61K031-4178**; **A61K031-4196**; **A61K031-43**; **A61K031-496**; **A61K031-513**; **A61K031-52**; **A61K031-522**; **A61K031-7048**; **A61K031-7056**; **A61K031-7072**; A61K047-10; A61K047-14; A61K047-28; A61K047-34; A61K047-36; A61K047-38; A61L015-16; A61M031-00; A61P015-00; A61P031-04; A61P031-10; A61P031-12; A61P033-02
AB WO 200203896 A UPAB: 20041011
NOVELTY - A method for treating vaginal or uterine fungal, bacterial, viral and parasitic infections is new.

DETAILED DESCRIPTION - A method for treating vaginal or uterine fungal, bacterial, viral and parasitic infections comprises contacting the vaginal epithelium with an intravaginal device medicated with an intravaginal or transvaginal composition comprising an active agent and an excipient. The active agent is an antifungal, parasiticidal, antibacterial or antiviral agent or trichomonicide and the excipient comprises a **lipophilic** or **hydrophilic** carrier, a mucoadhesive and a penetration enhancer or sorption promoter.

INDEPENDENT CLAIMS are also included for the following:

(1) a composition for intravaginal or transvaginal delivery for the treatment of fungal, viral, bacterial or parasitic infections comprising miconazole, terconazole, isoconazole, fenticonazole, fluconazole, nystatin, ketoconazole, clotrimazole, butoconazole, econazole, metronidazole, clindamycin, 5-fluoracil, aciclovir, AZT, famovir, penicillin, tetracycline or erythromycin in a vaginal suppository, bioadhesive tablet, bioadhesive microparticle, cream, lotion, foam, ointment, paste, solution or gel; and

(2) a device for intravaginal or transvaginal delivery of antifungal, antiviral, antibacterial or parasiticidal agents comprising a tampon, tampon-like device, vaginal ring, vaginal pessary, vaginal cup, vaginal tablet, vaginal suppository, vaginal sponge, vaginal bioadhesive tablet or vaginal bioadhesive microparticle comprising the agent as a cream, lotion, foam, ointment, solution or gel.

ACTIVITY - Fungicide; Antibacterial; Virucide; Antiparasitic;

Uropathic; Gynecological.
MECHANISM OF ACTION - None given in the source material.
USE - The method is useful for treating vaginal or uterine fungal, bacterial, viral and parasitic infections.
Dwg.0/19

FS CPI GMPI
FA AB; DCN
MC CPI: **A12-V01**; A12-V03A; B02-E; B02-T; **B04-C03C**; B06-D02; B06-D09; B07-H; B10-C04E; B10-E04C; B12-M02; B12-M03; B12-M07; B12-M08; B12-M09; B12-M11; B14-A01; B14-A02; B14-A03; B14-A03D; B14-A04; C02-E; C02-T; **C04-C03C**; C06-D02; C06-D09; C07-H; C10-C04E; C10-E04C; C12-M02; C12-M03; C12-M07; C12-M09; C12-M11; C14-A01; C14-A02; C14-A03; C14-A03D; C14-A04; D09-A01; F04-C01; F04-E04

L74 ANSWER 11 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2001-496568 [54] WPIX
DNC C2001-149074
TI Compositions useful in treatment of obesity include luminal cholecystokinin releasing factor coupled to an amphiphilic polymer, which exhibits improved pharmacokinetic properties.
DC A25 A96 B04 D16
IN **EKWURIBE, N N**; **EKWURIBE, N**
PA (NOBE-N) **NOBEX CORP**; (EKWU-I) EKWURIBE N
CYC 95
PI WO 2001041812 A2 20010614 (200154)* EN 49 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2001020875	A	20010618	(200161)		A61K047-48	<--
BR 2000016339	A	20020827	(200265)		A61K047-48	<--
NO 2002002793	A	20020813	(200266)		A61K000-00	
EP 1237580	A2	20020911	(200267)	EN	A61K047-48	<--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR						
CZ 2002001990	A3	20021113	(200282)		A61K047-48	<--
KR 2002068053	A	20020824	(200309)		A61K047-48	<--
JP 2003516366	W	20030513	(200334)	59	A61K047-48	<--
HU 2003000133	A2	20030528	(200341)		A61K047-48	<--
CN 1434725	A	20030806	(200366)		A61K047-48	<--
US 6638906	B1	20031028	(200372)		A01N037-18	
MX 2002005885	A1	20021101	(200376)		A61K047-48	<--
ZA 2002004603	A	20031126	(200402)	71	A61K000-00	
NZ 519489	A	20040130	(200414)		A61K047-48	<--
US 2004092449	A1	20040513	(200432)		A61K038-17	<--

ADT WO 2001041812 A2 WO 2000-US33592 20001211; AU 2001020875 A AU 2001-20875 20001211; BR 2000016339 A BR 2000-16339 20001211, WO 2000-US33592 20001211; NO 2002002793 A WO 2000-US33592 20001211, NO 2002-2793 20020612; EP 1237580 A2 EP 2000-984215 20001211, WO 2000-US33592 20001211; CZ 2002001990 A3 WO 2000-US33592 20001211, CZ 2002-1990 20001211; KR 2002068053 A KR 2002-707500 20020612; JP 2003516366 W WO 2000-US33592 20001211, JP 2001-543156 20001211; HU 2003000133 A2 WO 2000-US33592 20001211, HU 2003-133 20001211; CN 1434725 A CN 2000-818964 20001211; US 6638906 B1 US 1999-459443 19991213; MX 2002005885 A1 WO 2000-US33592 20001211, MX 2002-5885 20020612; ZA 2002004603 A ZA 2002-4603 20020607; NZ 519489 A NZ 2000-519489 20001211, WO 2000-US33592 20001211; US 2004092449 A1 Div ex US 1999-459443 19991213, US 2003-633966 20030804
FDT AU 2001020875 A Based on WO 2001041812; BR 2000016339 A Based on WO 2001041812; EP 1237580 A2 Based on WO 2001041812; CZ 2002001990 A3 Based on WO 2001041812; JP 2003516366 W Based on WO 2001041812; HU 2003000133 A2 Based on WO 2001041812; MX 2002005885 A1 Based on WO 2001041812; NZ 519489 A Based on WO 2001041812; US 2004092449 A1 Div ex US 6638906
PRAI US 1999-459443 19991213; US 2003-633966 20030804
IC ICM A01N037-18; A61K000-00; **A61K038-17**; **A61K047-48**
ICS A61P003-04; **C07K014-595**; C08G063-48; C08G063-91
AB WO 200141812 A UPAB: 20040210
NOVELTY - Compositions which include luminal cholecystokinin releasing factor (LCRF) coupled to amphiphilic polymers are new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for the following:
(1) LCRF composition comprising LCRF coupled with one or more molecules of a non-naturally occurring polymer. The polymer comprises a **lipophilic** group and a **hydrophilic** polymer group,

therefore imparting both **lipophilic** and **hydrophilic** characteristics to the composition so that the composition is soluble in pharmaceutical solvents and is able to interact with biological membranes;

(2) peptide composition comprising LCRF coupled with one or more molecules of a non-naturally occurring polymer which comprises a LM and a **hydrophilic** moiety. The composition is soluble in aqueous solvents and the LCRF is active in treatment or prevention of obesity;

(3) LCRF composition comprising LCRF covalently coupled with one or more molecules of a polymer which comprises a linear polyalkylene glycol group and a **lipophilic** group. The peptide and components are conformationally arranged such that the LCRF has an enhanced in vivo resistance to enzymatic degradation, relative to LCRF alone;

(4) multiligand conjugated LCRF complex comprising a triglyceride backbone group. The LCRF is covalently coupled with the triglyceride backbone group through a polyalkylene glycol spacer group which is bonded at a carbon atom of the triglyceride backbone. At least one fatty acid is covalently attached to a carbon atom of the triglyceride backbone group or is covalently joined through a polyalkylene glycol spacer group;

(5) stable, aqueous-soluble, conjugated LCRF complex which comprises a LCRF conjugatively coupled to a glycolipid group modified with polyethylene glycol;

(6) polysorbate complex comprising a polysorbate group which includes a triglyceride backbone which has a fatty acid group covalently coupled to one of the alpha , alpha ' or beta carbon atoms and a polyethylene glycol group covalently coupled to one of the alpha , alpha ' or beta carbon atoms. A physiologically active moiety can be covalently bonded to the polyethylene glycol group;

(7) compounds of formula (I):

X = N, O or S;

Y = LCRF or a protein;

n = 3 - 230; and

m = 0 - 20.

ACTIVITY - Anorectic. No biodata is provided.

MECHANISM OF ACTION - Luminal cholecystokinin releasing factor receptor agonist.

USE - The materials are useful for delivery of LCRF to receptors in the gut. LCRF is capable of stimulating release of cholecystokinin, a polypeptide hormone that induces satiety and reduces food intake. The materials may thus be used in treatment or prevention of obesity. Other peptides may be used in place of LCRF in the materials, so that they could be used for delivery of peptides useful in treatment of other disorders.

ADVANTAGE - The materials are stable and soluble in aqueous solutions. They may exhibit prolonged blood circulation and can be conformationally arranged so that the LCRF has enhanced in vivo resistance to enzymatic degradation. The conjugates can also deliver LCRF to receptors in the gut without absorption into the bloodstream.

Dwg.0/3

FS CPI

FA AB; DCN

MC CPI: A10-E08; **A12-V01**; **B04-C03D**; B04-H01; B04-J13; **B04-K01**; B12-M05; B14-E12; B14-L01; D05-H10

L74 ANSWER 12 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-335428 [35] WPIX

CR 2003-040529 [03]

DNC C2001-103553

TI New taxane prodrugs comprising polyethylene glycol units attached to a taxane by a hydrolyzable bond, useful for treating cancers.

DC A25 A96 B02 B07

IN BARTLEY, G S; **EKWURIBE, N N**; **PRICE, C H**; **PRICE, C**; **EKWURIBE, N**

PA (NOBE-N) **NOBEX CORP**; (BART-I) BARTLEY G S; (EKWU-I) EKWURIBE N N; (PRIC-I) PRICE C H

CYC 95

PI WO 2001019407 A2 20010322 (200135)* EN 57 A61K047-48 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000069512 A 20010417 (200140) A61K047-48 <--

US 2002013484 A1 20020131 (200210) C07D305-14

US 6380405 B1 20020430 (200235) C07D305-14

NO 2002001212 A 20020513 (200239) A61K000-00

BR 2000013949 A 20020514 (200240) A61K047-48 <--

EP 1214096 A2 20020619 (200240) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2002000929 A3 20020814 (200263) A61K047-48 <--
JP 2003509386 W 20030311 (200319) 74 A61K031-337 <--
KR 2002082458 A 20021031 (200319) A61K047-48 <--
CN 1390142 A 20030108 (200334) A61K047-48 <--
HU 2003000093 A2 20030528 (200341) A61K047-48 <--
ZA 2002002040 A 20030827 (200362) 92 A61K000-00
MX 2002002711 A1 20020801 (200367) A61K047-48 <--
US 2003203961 A1 20031030 (200372) A61K031-337 <--
NZ 517680 A 20031219 (200404) A61K047-48 <--

ADT WO 2001019407 A2 WO 2000-US24523 20000907; AU 2000069512 A AU 2000-69512 20000907; US 2002013484 A1 Provisional US 1999-153579P 19990913, CIP of US 1999-476974 19991231, US 2001-802739 20010309; US 6380405 B1 Provisional US 1999-153579P 19990913, US 1999-476974 19991231; NO 2002001212 A WO 2000-US24523 20000907, NO 2002-1212 20020312; BR 2000013949 A BR 2000-13949 20000907, WO 2000-US24523 20000907; EP 1214096 A2 EP 2000-957966 20000907, WO 2000-US24523 20000907; CZ 2002000929 A3 WO 2000-US24523 20000907, CZ 2002-929 20000907; JP 2003509386 W WO 2000-US24523 20000907, JP 2001-523038 20000907; KR 2002082458 A KR 2002-703277 20020312; CN 1390142 A CN 2000-815507 20000907; HU 2003000093 A2 WO 2000-US24523 20000907, HU 2003-93 20000907; ZA 2002002040 A ZA 2002-2040 20020312; MX 2002002711 A1 WO 2000-US24523 20000907, MX 2002-2711 20020312; US 2003203961 A1 Provisional US 1999-153579P 19990913, CIP of US 1999-476974 19991231, Cont of US 2001-802739 20010309, US 2003-395548 20030324; NZ 517680 A NZ 2000-517680 20000907, WO 2000-US24523 20000907

FDT AU 2000069512 A Based on WO 2001019407; BR 2000013949 A Based on WO 2001019407; EP 1214096 A2 Based on WO 2001019407; CZ 2002000929 A3 Based on WO 2001019407; JP 2003509386 W Based on WO 2001019407; HU 2003000093 A2 Based on WO 2001019407; MX 2002002711 A1 Based on WO 2001019407; US 2003203961 A1 CIP of US 6380405, Cont of US 6541508; NZ 517680 A Based on WO 2001019407

PRAI US 1999-476974 19991231; US 1999-153579P 19990913;
US 2001-802739 20010309; US 2003-395548 20030324

IC ICM A61K000-00; **A61K031-337**; **A61K047-48**; C07D305-14
ICS A61K009-08; A61K009-10; A61K009-14; A61K009-20; A61K009-48; A61P013-12; A61P033-06; A61P035-00; A61P035-02; A61P043-00

AB WO 200119407 A UPAB: 20040115

NOVELTY - New taxane prodrugs comprising polyethylene glycol units attached to a taxane by a hydrolyzable bond, useful for treating cancers are disclosed.

DETAILED DESCRIPTION - A novel taxane prodrug comprises: (a) at least one taxane; and (b) one or more polyethylene (PEG) polymers and/or oligomers, each joined to a bonding site on the therapeutic compound by a hydrolyzable bond, the PEG polymers and/or oligomers each: (i) comprising a straight or branched PEG segment consisting of 2 to 25 PEG units; and (ii) optionally comprising a salt-forming moiety.

An INDEPENDENT CLAIM is also included for a taxane prodrug comprising a taxane joined by hydrolyzable bond(s) to one or more PEG oligomer(s) selected from: formula (II)-(XI): -CO-(CH2)n-NR-CH2CH2(OC2H4)mOCH3 (II);
-CO-(CH2)n1-CO-NH-(CH2)p-NR-CH2CH2(OC2H4)mOCH3 (III);
-CO-(CH2)n1-CO-NH-(CH2CH2(OC2H4)r-NR-CH2CH2(OC2H4)mOCH3 (IV);
-CO-(CH2)n1-CO-NH-(CH2)p-NR-CH2CH2(OC2H4)mNH2 (V);
-CO-(CH2)n1-CO-NH-(CH2)p-NR-CH2CH2(OC2H4)mNH3+X- (VI);
-CO-(CH2)n1-CO-NH-(CH2)p-NR1-CH2CH2(OC2H4)mNHR2 (VII);
-CO-(CH2)n1-CO-NH-CH2CH2(OC2H4)mOCH2-C(=O)-NH(CH2)pN(CH3)2 (VIII);
-CO-(CH2)n1(OC2H4)mO(CH2)p1-C(=O)-O-Y+ (IX);
-CO-(CH2)n2-NR1R2-CH2CH2(OC2H4)mOCH3 (X);

n = 1-7;
m = 2-25;
n1 = 1-6;
p = 2-8;
R, R1, R2 = lower alkyl;
r = 2-25
X- = a negative ion;
p1 = 1-6;
Y+ = a positive ion
n2 = 1-5;
q = 1-6.

USE - The compositions can be used to treat cancers, tumors, malignancies, uncontrolled tissue or cellular proliferation secondary to tissue injury, polycystic kidney disease or malaria (claimed). They can be used to treat hepatocellular carcinoma, liver metastases, cancers of the gastrointestinal tract, pancreas, kidney, colon, cervix, prostate, lung,

leukemia and Kaposi's sarcoma, renal, colon, cervix, prostate or melanoma (claimed).

ADVANTAGE - The taxane-oligomer conjugates exhibit improved solubility characteristics, improved oral bioavailability, and an improved pharmacokinetic profile.

Dwg.0/2

FS CPI

FA AB; GI; DCN

MC CPI: A10-E01; **A12-V01**; B02-D; **B04-C03C**; B05-A03B; B05-C01; B05-C07; B06-A03; B07-D04A; B10-B03B; B10-C04D; B14-A03B; B14-H01; B14-N10

L74 ANSWER 13 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-335427 [35] WPIX

DNC C2001-103552

TI New prodrugs comprising polyethylene glycol units attached to a therapeutic compound by a hydrolyzable bond, useful for the delivery of agents such as etoposide for treating cancer.

DC A25 A96 B02 B07

IN DYAKONOV, T A; **EKWURIBE, N N**; **PRICE, C H**; **EKWURIBE, N**

PA (NOBE-N) **NOBEX CORP**; (DYAK-I) DYAKONOV T A; (EKWU-I) EKWURIBE N; (PRIC-I) PRICE C H

CYC 95

PI WO 2001019406 A2 20010322 (200135)* EN 57 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000075756 A 20010417 (200140) A61K047-48 <--
EP 1212099 A2 20020612 (200239) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
NO 2002001213 A 20020513 (200239) A61K000-00
BR 2000013948 A 20020514 (200240) A61K047-48 <--
CZ 2002000928 A3 20020911 (200268) A61K047-48 <--
KR 2002059398 A 20020712 (200306) A61K047-48 <--
JP 2003509385 W 20030311 (200319) 73 A61K047-48 <--
CN 1390143 A 20030108 (200334) A61K047-48 <--
HU 2002004110 A2 20030428 (200337) A61K047-48 <--
ZA 2002002039 A 20030827 (200362) 89 A61K000-00
NZ 517681 A 20040130 (200414) A61K047-48 <--
US 6713454 B1 20040330 (200423) A61K031-704 <--
US 2004180840 A1 20040916 (200461) A61K031-7048 <--

ADT WO 2001019406 A2 WO 2000-US24520 20000907; AU 2000075756 A AU 2000-75756 20000907; EP 1212099 A2 EP 2000-964949 20000907, WO 2000-US24520 20000907; NO 2002001213 A WO 2000-US24520 20000907, NO 2002-1213 20020312; BR 2000013948 A BR 2000-13948 20000907, WO 2000-US24520 20000907; CZ 2002000928 A3 WO 2000-US24520 20000907, CZ 2002-928 20000907; KR 2002059398 A KR 2002-703276 20020312; JP 2003509385 W WO 2000-US24520 20000907, JP 2001-523037 20000907; CN 1390143 A CN 2000-815508 20000907; HU 2002004110 A2 WO 2000-US24520 20000907, HU 2002-4110 20000907; ZA 2002002039 A ZA 2002-2039 20020312; NZ 517681 A NZ 2000-517681 20000907, WO 2000-US24520 20000907; US 6713454 B1 Provisional US 1999-153649P 19990913, US 1999-474915 19991231; US 2004180840 A1 Provisional US 1999-153649P 19990913, Div ex US 1999-474915 19991231, US 2004-808044 20040324

FDT AU 2000075756 A Based on WO 2001019406; EP 1212099 A2 Based on WO 2001019406; BR 2000013948 A Based on WO 2001019406; CZ 2002000928 A3 Based on WO 2001019406; JP 2003509385 W Based on WO 2001019406; HU 2002004110 A2 Based on WO 2001019406; NZ 517681 A Based on WO 2001019406; US 2004180840 A1 Div ex US 6713454

PRAI US 1999-474915 19991231; US 1999-153649P 19990913; US 2004-808044 20040324

IC ICM A61K000-00; **A61K031-704**; **A61K031-7048**; **A61K047-48**
ICS A23L001-30; A61K009-08; A61K009-107; A61K009-14; A61K009-20; A61K009-48; **A61K031-337**; A61P035-00; A61P035-02; A61P035-04; A61P043-00; C07H015-08; C08G063-48

AB WO 200119406 A UPAB: 20010625

NOVELTY - New prodrugs comprising polyethylene glycol units attached to a therapeutic compound by a hydrolyzable bond, useful for the delivery of agents such as etoposide for treating cancer are disclosed.

DETAILED DESCRIPTION - A novel prodrug comprises: (a) at least one

therapeutic compound; and (b) one or more polyethylene glycol (PEG) polymers and/or oligomers, each joined to a bonding site on the therapeutic compound by a hydrolyzable bond, the PEG polymers and/or oligomers each: (i) comprising a straight or branched PEG segment consisting of 2 to 25 PEG units; and (ii) optionally comprising a salt-forming moiety.

An INDEPENDENT CLAIM is also included for a prodrug comprising a therapeutic compound joined by hydrolyzable bond(s) to one or more PEG oligomer(s) selected from formula (II)-(XI): -CO-(CH2)n-NR-CH2CH2(OC2H4)mOCH3 (II);

-CO-(CH2)n1-CO-NH-(CH2)p-NR-CH2CH2(OC2H4)mOCH3 (III);

-CO-(CH2)n1-CO-NH-CH2CH2(OC2H4)r-NR-CH2CH2(OC2H4)mOCH3 (IV);

-CO-(CH2)n1-CO-NH-(CH2)p-NR-CH2CH2(OC2H4)mNH2 (V);

-CO-(CH2)n1-CO-NH-(CH2)p-NR-CH2CH2(OC2H4)mNH3+X- (VI);

-CO-(CH2)n1-CO-NH-(CH2)p-NR1-CH2CH2(OC2H4)mNHR2 (VII);

-CO-(CH2)n1-CO-NH-CH2CH2(OC2H4)mOCH2-CO-NH-(CH2)pN(CH3)2 (VIII);

-CO-(CH2)n1(OC2H4)mO(CH2)p1-C(=O)-O-Y+ (IX);

-CO-(CH2)n2-NR1R2-CH2CH2(OC2H4)mOCH3 (X);

n = 1-7;

m = 2-25;

R, R1, R2 = lower alkyl

n1 = 1-6;

p = 2-8;

r = 2-25;

X- = = a negative ion;

p1 = 1-6;

Y+ = a positive ion;

q = 1-5.

USE - The prodrugs can be used for the delivery of drugs such as etoposide. The compositions can be used to treat cancers, tumors or malignancies, e.g. small cell lung cancer, non-small cell lung cancer, testicular cancer, lymphoma, leukemia, ovarian cancer or gastric cancer (claimed).

ADVANTAGE - The prodrugs increase the amphiphilicity of the drugs and facilitate the formation of drugs, the oral delivery of drugs, and the delivery of drugs across the blood brain barrier.

Conjugates of etoposide with PEG was administered intravenously to Sprague-Dawley rats at a dosage of 9 micro mole/kg. Measurement of free etoposide in plasma at various time points demonstrated that peak plasma etoposide concentration was increased by 60% and the half life was extended by approx. 50% in rats given the etoposide conjugate versus rats given etoposide. When the etoposide concentration in brain tissue was measured in these rats the data revealed that injection with the etoposide conjugate led to a 3-fold increase in accumulation of free etoposide in the brain parenchyma. These data agree with other studies demonstrating an increased penetration of the blood-brain barrier by conjugated peptide hormones.

Dwg.0/6

FS CPI

FA AB; GI; DCN

MC CPI: A10-E01; **A12-V01**; **B04-C03C**; B06-A02; B06-A03; B07-D04A; B10-B03B; B10-C04D; B12-M11; B14-H01

L74 ANSWER 14 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2001-102601 [11] WPIX

DNC C2001-029994

TI New drug-oligomer conjugates facilitate oral delivery of e.g. insulin, and can delay the onset of activity or extend the duration of activity of drug in the bloodstream.

DC A96 B04 C03

IN **EKWURIBE, N**; RAJAGOPALAN, J; RAMASWAMY, M; **EKWURIBE, N N**; RAJAGOPALAN, J S

PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) **NOBEX CORP**; (NOBE-N) **NOBEX INC**

CYC 95

PI WO 2000078302 A1 20001228 (200111)* EN 69 A61K031-075 <--

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000057500 A 20010109 (200122)

US 6309633 B1 20011030 (200172) A61K009-107

NO 2001006143 A 20020218 (200228) A61K000-00

BR 2000011772 A 20020402 (200231) A61K031-075 <--

EP 1196157 A1 20020417 (200233) EN A61K031-075 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
CZ 2001004597 A3 20020515 (200241) A61K031-075 <--
KR 2002012278 A 20020215 (200257) A61K047-48 <--
CN 1368877 A 20020911 (200282) A61K031-075 <--
JP 2003502364 W 20030121 (200308) 68 A61K047-48 <--
HU 2002003745 A1 20030428 (200337) A61K031-075 <--
ZA 2001010099 A 20030528 (200341) 80 A61K000-00
MX 2002000054 A1 20030701 (200366) A61K031-075 <--
NZ 516109 A 20040430 (200431) A61K031-075 <--

ADT WO 2000078302 A1 WO 2000-US16879 20000619; AU 2000057500 A AU 2000-57500 20000619; US 6309633 B1 US 1999-336548 19990619; NO 2001006143 A WO 2000-US16879 20000619, NO 2001-6143 20011217; BR 2000011772 A BR 2000-11772 20000619, WO 2000-US16879 20000619; EP 1196157 A1 EP 2000-942956 20000619, WO 2000-US16879 20000619; CZ 2001004597 A3 WO 2000-US16879 20000619, CZ 2001-4597 20000619; KR 2002012278 A KR 2001-716204 20011217; CN 1368877 A CN 2000-811540 20000619; JP 2003502364 W WO 2000-US16879 20000619, JP 2001-504366 20000619; HU 2002003745 A1 WO 2000-US16879 20000619, HU 2002-3745 20000619; ZA 2001010099 A ZA 2001-10099 20011207; MX 2002000054 A1 WO 2000-US16879 20000619, MX 2002-54 20011219; NZ 516109 A NZ 2000-516109 20000619, WO 2000-US16879 20000619

FDT AU 2000057500 A Based on WO 2000078302; BR 2000011772 A Based on WO 2000078302; EP 1196157 A1 Based on WO 2000078302; CZ 2001004597 A3 Based on WO 2000078302; JP 2003502364 W Based on WO 2000078302; HU 2002003745 A1 Based on WO 2000078302; MX 2002000054 A1 Based on WO 2000078302; NZ 516109 A Based on WO 2000078302

PRAI US 1999-336548 19990619

IC ICM A61K000-00; A61K009-107; **A61K031-075**; **A61K047-48**
ICS **A61K031-13**; **A61K031-16**; **A61K031-21**; **A61K031-325**; **A61K038-00**; **A61K038-02**; **A61K038-17**; **A61K038-22**; **A61K038-28**; A61K039-385; A61P003-10; **C07K001-113**

AB WO 200078302 A UPAB: 20010224
NOVELTY - Drug-oligomer conjugates (I) which include a **hydrophilic** component and a **lipophilic** component liked by a hydrolyzable bond, are new.

DETAILED DESCRIPTION - Drug-oligomer conjugates (I), (X), (XI), (XII) and (XIII), which include a **hydrophilic** component and a **lipophilic** component liked by a hydrolyzable bond, are new.

D = therapeutic drug moiety;

H, H' = **hydrophilic** moieties selected from straight or branched polyethylene glycol (PEG) polymers which have 2-130 ethylene glycol subunits and sugars;

L = **lipophilic** moiety selected from 2-24C alkyl groups, cholesterol and fatty acids;

m + n + p = at least one, but does not exceed the total number of covalent bonding sites on D for the substituents H', L and H-L;

o (defined in the disclosure) = 1 to the maximum number of covalent binding sites on H; and

L' (defined in the disclosure) = L.

INDEPENDENT CLAIMS are included for:

(1) drug-oligomer conjugate of formula (XI), in which the S-L and/or S-H bond is hydrolyzable;

(2) drug-oligomer conjugates of formula (XII), in which the S-H and/or S-H' bond is hydrolyzable;

(3) drug-oligomer conjugates of formula (XIII), in which the H-H' bond is hydrolyzable;

(4) drug-oligomer conjugates of formula (X), in which the H-H' bond is hydrolyzable; and

(5) method of providing to a subject an active drug-PEG conjugate of formula (X), in which the H-H' bond is hydrolyzable and the H'L bond is not hydrolyzable, D is insulin or a derivative, where (X) has enhanced activity compared to unconjugated insulin.

S = spacer group selected from sugars, carbohydrates and glycerol;

n = 1 to the maximum number of covalent binding sites at which S can be attached to H;

o = 1 to the maximum number of covalent binding sites at which L can be attached to S;

p = 1 to the maximum number of covalent binding sites at which ((H-Sn)Lo)p can be attached to D; and

q = 1 to the maximum number of covalent binding sites at which H' can be attached to S.

ACTIVITY - Antidiabetic; virucide; antibacterial.

MECHANISM OF ACTION - None given.

USE - The new conjugates can be used in treatment or prevention of

any disorders which can be treated by the therapeutic drug D, including bacterial and viral infections. Drug D is preferably insulin, useful in treatment of diabetes.

ADVANTAGE - The new conjugates contain **hydrophilic** components, **lipophilic** components and drug components. These components are variously linked such that, upon hydrolysis of hydrolyzable bonds in the conjugates, an active drug-**hydrophile** conjugate remains. The oligomers are very suitable for oral delivery, while extending the onset of activity of drug-oligomer conjugate in the blood stream. The **lipophilic** component is preferably selected such that the drug component is inactive until the hydrolyzable bond is hydrolysed. Amphiphilic modification of insulin improves its **lipophilicity** and stabilizes it against enzymatic degradation while improving its membrane permeability.

Dwg.0/3

FS CPI

FA AB; GI; DCN

MC CPI: A10-E01; **A12-V01**; B01-D02; **B04-C03C**; B04-D01; B04-J03A; B04-N04; B09-D01; B14-A01; B14-A02; B14-F09; C01-D02; **C04-C03C**; **C04-D01**; **C04-J03A**; **C04-N04**; C09-D01; C14-A01; C14-A02; C14-F09

L74 ANSWER 15 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN

AN 2000-544632 [50] WPIX

DNC C2000-162252

TI Protecting cells against chemical agents, useful in conjunction with e.g. cytostatic or antiviral agents, by treatment with peptide derived from Bowman-Birk protease inhibitor.

DC B04 B05 D16

IN DITTMANN, K; GUEVEN, N; MAYER, C; RODEMANN, H P

PA (UYTU-N) UNIV TUEBINGEN EBERHARD-KARLS

CYC 23

PI

DE 19906108	A1 20000817 (200050)*		15	A61K038-56	<--
WO 2000047217	A2 20000817 (200050)	GE		A61K038-00	<--
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA JP US					
AU 2000029084	A 20000829 (200062)			A61K038-00	<--
EP 1150705	A2 20011107 (200168)	GE		A61K038-56	<--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
EP 1150705	B1 20040526 (200435)	GE		A61K038-56	<--
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
DE 50006591	G 20040701 (200443)			A61K038-56	<--

ADT DE 19906108 A1 DE 1999-1006108 19990213; WO 2000047217 A2 WO 2000-EP1006 20000208; AU 2000029084 A AU 2000-29084 20000208; EP 1150705 A2 EP 2000-907521 20000208, WO 2000-EP1006 20000208; EP 1150705 B1 EP 2000-907521 20000208, WO 2000-EP1006 20000208; DE 50006591 G DE 2000-00006591 20000208, EP 2000-907521 20000208, WO 2000-EP1006 20000208

FDT AU 2000029084 A Based on WO 2000047217; EP 1150705 A2 Based on WO 2000047217; EP 1150705 B1 Based on WO 2000047217; DE 50006591 G Based on EP 1150705, Based on WO 2000047217

PRAI DE 1999-19906108 19990213

IC ICM **A61K038-00**; **A61K038-56**

ICS **A61K047-48**; A61K048-00; A61P043-00

ICA C07K014-81; C12N005-10

AB DE 19906108 A UPAB: 20001010

NOVELTY - Protecting cells during in vivo or in vitro treatment with a chemical agent (I) by using at least 1 peptide (II) that is a modified form, and/or optionally modified fragment, of the Bowman-Birk protease inhibitor (BBI), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) similar use of a nucleic acid (III) containing a segment that encodes at least 1 (II); and

(2) a pharmaceutical composition containing (II) or (III) in a sufficient amount to protect cells against cytostatic, immunosuppressant and/or virostatic agents.

ACTIVITY - Cytoprotective. The peptide CALSYPAQC (P1) was incubated, at 80 micro M, with normal human fibroblasts for 16 hours, before treatment of the cells for 1 hour with cis-platin at 1 mu g/ml. The cells were washed, incubated for various times (t) in normal medium, then transferred to serum-containing medium for clonogenic assay. For all values of t, the clonogenic survival rate was higher for cells treated with P1 than for controls, e.g. where t = 6 hours, the rate was about 48% for treated cells and about 28% for controls. A similar test with spontaneously transformed fibroblasts (carrying a mutation in the p53 gene) showed that P1 did not protect transformed cells.

MECHANISM OF ACTION - None given.
USE - (II) are used to protect cells during exposure to cytostatic, virostatic or immunosuppressing agents, either in vivo (e.g. during treatment of tumors) or in vitro, e.g. purging leukemia cells from bone marrow or preparing organs for transplantation. Nucleic acid (III) that encode (II) can be used similarly, either in gene therapy or for in vitro cell transformation or transfection.
ADVANTAGE - (II) protect non-target cells (especially rapidly proliferating cells) against the damaging effects of (I), so side-effects are reduced without adverse effects on activity against target cells. This may allow a higher dose of (I) to be used. (II) retain the (radio)protective effects of complete BBI but, unlike BBI, do not significantly inhibit (chymo)trypsin or other serine proteases, so should not damage the pancreas. Since they are small, (II) penetrate cells and tissues quickly and well, and they are easy to prepare. (II) may be stabilized by alkylation, cyclization etc., and may be attached to a protein to extend their half-life in the blood.
Dwg.0/5

FS CPI
FA AB; DCN
MC CPI: **B04-C01B**; B04-E03; B04-E04; B04-M01; B14-G02; B14-H01; D05-H12A; D05-H12D5; D05-H17A

L74 ANSWER 16 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2000-423233 [36] WPIX
DNC C2000-128094
TI Supramolecular complexes comprising therapeutic agent and polydimensional polymer network, e.g. based on cyclodextrin, useful for delivery of therapeutic agents such as DNA.
DC A25 A26 A96 B07 D16
IN DAVIS, M E; GONZALEZ, H; HWANG, S
PA (CALY) CALIFORNIA INST OF TECHNOLOGY
CYC 89
PI WO 2000033885 A1 20000615 (200036)* EN 70 A61K047-48 <--
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW
AU 2000021627 A 20000626 (200045) A61K047-48 <--
EP 1133318 A1 20010919 (200155) EN A61K047-48 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
JP 2002531530 W 20020924 (200278) 71 A61K047-40
ADT WO 2000033885 A1 WO 1999-US28547 19991203; AU 2000021627 A AU 2000-21627 19991203; EP 1133318 A1 EP 1999-965967 19991203, WO 1999-US28547 19991203; JP 2002531530 W WO 1999-US28547 19991203, JP 2000-586375 19991203
FDT AU 2000021627 A Based on WO 2000033885; EP 1133318 A1 Based on WO 2000033885; JP 2002531530 W Based on WO 2000033885
PRAI US 1999-127856P 19990405; US 1998-110847P 19981204
IC ICM A61K047-40; **A61K047-48**
ICS **A61K031-335**; **A61K031-70**; **A61K045-00**; A61K047-32; A61K048-00
AB WO 200033885 A UPAB: 20000801
NOVELTY - Preparation of a supramolecular complex (I) involves contacting at least one therapeutic agent (A) and at least one polymer (II) to form a composite, and treating (II) in the composite to form (I), consisting of (A) and a polydimensional polymer network.
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for (I) obtained by the novel preparation method.
ACTIVITY - Anti-HIV; cytostatic; cardiant; tranquilizer; vulnerary; vasotropic; hemostatic.
MECHANISM OF ACTION - None given.
USE - (I) are useful as delivery vehicles for the administration of (A), which is specifically an antibiotic, steroid, polynucleotide, plasmid, peptide, peptide fragment, small molecule, chelating agent or biologically active macromolecule, especially DNA (claimed). Disorders to be treated include cystic fibrosis, Gaucher's disease, muscular dystrophy, AIDS, cancer (e.g. multiple myeloma, leukemia, melanoma or ovarian carcinoma), cardiovascular conditions, (e.g. progressive heart failure, restenosis or hemophilia) or neurological conditions (e.g. brain trauma). (A) may also be agrochemicals, e.g. fungicides, herbicides or insecticides.
ADVANTAGE - By incorporation in (I), (A) is protected against loss of activity (e.g. due to degradation) and given increased solubility and

bioavailability. A wide range of **lipophilic** or **hydrophilic**, synthetic or naturally occurring (A) can be incorporated.
Dwg.0/1

FS CPI
FA AB; DCN
MC CPI: A03-A00A; A05-J07; A08-D01; **A12-V01**; B04-E01; B04-E03; B04-E08; B04-N04; B11-C01; B12-M05; B14-A02B1; B14-F01; B14-F02D; B14-F04; B14-H01B; B14-J01B4; B14-N17B; D05-H10

L74 ANSWER 17 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 2000-256190 [22] WPIX
DNC C2000-078134
TI Amphiphilic drug-oligomer conjugate for delivery of therapeutic agents, used to treat central nervous system disorders, or diagnostic agents across the blood brain barrier.
DC A96 B04 B05
IN **ANDERSON, W R**; **ANSARI, A M**; **EKWURIBE, N N**; **PRICE, C H**; **RADHAKRISHNAN, B**; AUSARI, A M; **ANDERSON, W**; RHADAKRISHNAN, B
PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) **NOBEX CORP**; (NOBE-N) **NOBEX INC**; (ANDE-I) ANDERSON W R; (ANSA-I) ANSARI A M; (EKWU-I) EKWURIBE N N; (PRIC-I) PRICE C H; (RADH-I) RADHAKRISHNAN B
CYC 83
PI WO 2000009073 A2 20000224 (200022)* EN 75 A61K000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG US UZ VN YU ZW
AU 9956726 A 20000306 (200030)
EP 1105142 A2 20010613 (200134) EN A61K031-705 <--
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI
BR 9914280 A 20011113 (200201) A61K031-704 <--
KR 2001072472 A 20010731 (200209) A61K047-48 <--
CN 1323213 A 20011121 (200218) A61K031-704 <--
JP 2002522463 W 20020723 (200263) 78 A61K047-48 <--
MX 2001001694 A1 20020501 (200368) A61K000-00000
US 6703381 B1 20040309 (200418) A61K031-56 <--
US 2004102381 A1 20040527 (200435) A61K038-23 <--
US 2004110735 A1 20040610 (200438) A61K031-56 <--
AU 772494 B2 20040429 (200457) A61K031-705 <--
ADT WO 2000009073 A2 WO 1999-US18248 19990812; AU 9956726 A AU 1999-56726 19990812; EP 1105142 A2 EP 1999-943676 19990812, WO 1999-US18248 19990812; BR 9914280 A BR 1999-14280 19990812, WO 1999-US18248 19990812; KR 2001072472 A KR 2001-701888 20010213; CN 1323213 A CN 1999-812133 19990812; JP 2002522463 W WO 1999-US18248 19990812, JP 2000-564577 19990812; MX 2001001694 A1 WO 1999-US18248 19990812, MX 2001-1694 20010213; US 6703381 B1 US 1998-134803 19980814; US 2004102381 A1 Div ex US 1998-134803 19980814, US 2003-716578 20031119; US 2004110735 A1 Div ex US 1998-134803 19980814, US 2003-716975 20031119; AU 772494 B2 AU 1999-56726 19990812
FDT AU 9956726 A Based on WO 2000009073; EP 1105142 A2 Based on WO 2000009073; BR 9914280 A Based on WO 2000009073; JP 2002522463 W Based on WO 2000009073; MX 2001001694 A1 Based on WO 2000009073; US 2004102381 A1 Div ex US 6703381; US 2004110735 A1 Div ex US 6703381; AU 772494 B2 Previous Publ. AU 9956726, Based on WO 2000009073
PRAI US 1998-134803 19980814; US 2003-716578 20031119; US 2003-716975 20031119
IC ICM A61K000-00; A61K000-00000; **A61K031-56**; **A61K031-704**; **A61K031-705**; **A61K038-23**; **A61K047-48**
ICS **A61K038-00**; **A61K038-04**; **A61K038-11**; **A61K038-21**; **A61K038-22**; **A61K038-26**; **A61K038-27**; **A61K038-33**; **A61K038-36**; **A61K038-42**; **A61K038-46**; **A61K038-48**; A61K039-395; **A61K045-00**; A61P005-02; A61P005-10; A61P005-14; A61P005-18; A61P029-00; A61P043-00; **C07K014-70**; **C07K017-00**
AB WO 200009073 A UPAB: 20000508
NOVELTY - Amphiphilic drug-oligomer conjugate comprising a therapeutic compound conjugated to an oligomer comprising a **lipophilic** moiety coupled to a **hydrophilic** moiety, is new.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an amphiphilic oligomer-enkephalin conjugate selected from the group consisting of DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys, cetyl Met-enkephalin-Lys, cholesterol Met-enkephalin-Lys, palmitate-teg Met-enkephalin-Lys, and di-palmitate-teg Met-enkephalin-Lys;

(2) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a **lipophile** coupled to a **hydrophile** by a hydrolyzable bond, the conjugate being DHA Met-enkephalin-Lys, linoleic Met-enkephalin-Lys or cetyl Met-enkephalin-Lys;

(3) an amphiphilic oligomer-enkephalin conjugate where the oligomer comprises a **lipophile** coupled to a **hydrophile** by a non-hydrolyzable bond, the conjugate being cholesterol Met-enkepahlin-Lys, palmitate-teg Met-enkephalin-Lys or di-palmitate-teg Met-enkephalin-Lys;

(4) a method for activating a receptor comprising bringing the receptor into contact with the novel conjugate;

(5) a method for delivering a therapeutic compound across the blood-brain barrier comprising administering the novel conjugate;

(6) a method for inducing analgesia in a subject, comprising administering the novel conjugate; and

(7) a method for altering the binding affinity of a peptide or protein to its receptor, comprising conjugating the peptide to the novel conjugate.

ACTIVITY - Cerebroprotective.

MECHANISM OF ACTION - None given.

USE - The conjugates are capable of traversing the blood-brain barrier and so delivering therapeutic agents used in the treatment of disease states associated with the central nervous system (CNS) or for delivering diagnostic agents across the blood brain barrier.

ADVANTAGE - The conjugates are stable in the bloodstream and resist degradation by the enzymes of the blood brain barrier and in the CNS. The conjugates readily cross the blood brain barrier.

Dwg.0/10

FS CPI
FA AB; DCN
MC CPI: **A12-V01**; B01-D02; **B04-C01B**; B12-K04; B14-J01

L74 ANSWER 18 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1999-469300 [39] WPIX
DNC C1999-137742
TI Agent for transfer of nucleic acid containing cationic **hydrophilic** and **lipophilic** regions, e.g. for gene therapy.
DC A96 B04 B05 D16
IN BYK, G; DUBERTRET, C; PITARD, B; SCHERMAN, D
PA (RHON) RHONE-POULENC RORER SA; (AVET) AVENTIS PHARMA SA
CYC 77
PI WO 9938821 A2 19990805 (199939)* FR 51 C07C000-00
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AT BA BB BG BR CA CN CU CZ EE GD GE HU ID IL IN IS JP KP KR LC LK LR LT LV MG MK MN MX NO NZ PL RO RU SG SI SK SL TR TT UA US UZ VN YU
FR 2774394 A1 19990806 (199939) C12N015-88
ZA 9900694 A 19991027 (199951) 75 C08L000-00
NO 2000003880 A 20000728 (200056) C07C000-00
EP 1049793 A2 20001108 (200062) FR C12N015-87
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT SE SI
CZ 2000002713 A3 20001115 (200064) C12N015-87
AU 2000043843 A 20010405 (200125) C07C019-00
BR 9907269 A 20010403 (200128) C12N015-87
CN 1289371 A 20010328 (200140) C12N015-87
HU 2001001393 A2 20010828 (200157) C12N015-87
JP 2002501762 W 20020122 (200211) 61 C12N015-09
KR 2001081924 A 20010829 (200215) C12N015-87
MX 2000007036 A1 20011201 (200282) A61K048-00
US 6521252 B1 20030218 (200317) A61K009-127
AU 759197 B 20030410 (200337) C07C019-00
ADT WO 9938821 A2 WO 1999-FR162 19990128; FR 2774394 A1 FR 1998-1065 19980130; ZA 9900694 A ZA 1999-694 19990128; NO 2000003880 A WO 1999-FR162 19990128, NO 2000-3880 20000728; EP 1049793 A2 EP 1999-901639 19990128, WO 1999-FR162 19990128; CZ 2000002713 A3 WO 1999-FR162 19990128, CZ 2000-2713 19990128; AU 2000043843 A AU 2000-43843 20000704; BR 9907269 A BR 1999-7269 19990128, WO 1999-FR162 19990128; CN 1289371 A CN 1999-802464 19990128; HU 2001001393 A2 WO 1999-FR162 19990128, HU 2001-1393 19990128; JP 2002501762 W WO 1999-FR162 19990128, JP 2000-530060 19990128; KR 2001081924 A KR 2000-708257 20000728; MX 2000007036 A1 MX 2000-7036 20000718; US 6521252 B1 Provisional US 1998-77026P 19980306, Cont of WO 1999-FR162 19990128, US 2000-610727 20000706; AU 759197 B AU 2000-43843

20000704
FDT EP 1049793 A2 Based on WO 9938821; CZ 2000002713 A3 Based on WO 9938821; BR 9907269 A Based on WO 9938821; HU 2001001393 A2 Based on WO 9938821; JP 2002501762 W Based on WO 9938821; AU 759197 B Previous Publ. AU 2000043843
PRAI US 1998-77026P 19980306; FR 1998-1065 19980130
IC ICM A61K009-127; A61K048-00; C07C000-00; C07C019-00; C08L000-00; C12N015-09; C12N015-87; C12N015-88
ICS **A61K031-7105**; **A61K031-711**; **A61K038-05**; **A61K047-48**; A61P043-00; C07C323-60; **C07K005-062**
AB WO 9938821 A UPAB: 19990928
NOVELTY - Agent (I) for transfer of nucleic acid (II) comprises:
(a) at least one cationic **hydrophilic** region that can associate non-covalently with (II); and
(b) at least one **lipophilic** region.
These regions are linked by a spacer arm that also includes at least one disulfide bridge such that reduction causes:
(a) partial degradation of the **lipophilic** region; or
(b) splitting of (I) into two where this is symmetrical.
DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:
(1) composition containing (I) and at least one (II); and
(2) preparation of the compositions of (1).
ACTIVITY - None given.
MECHANISM OF ACTION - None given.
USE - (I) are used to deliver (II) to cells, in vitro, in vivo or ex vivo, e.g. for production of recombinant proteins, to screen for regulators of gene expression, for cloning, to produce transgenic animals, for vaccination, for gene therapy, for immunotherapy etc.
ADVANTAGE - The **hydrophilic** part of (I) provides efficient complexation with (I) and the **lipophilic** part renders this ionic interaction insensitive to the external medium, by covering the particle formed with a lipid layer. When the disulfide bond is reduced, a detergent, able to destabilize membranes, is generated, so a greater quantity of nucleic acid can be transported to the transcriptional machinery of the host cell. (I) have an inherently low toxicity, provide efficient transfer (and are thus required only in small amounts) and increase serum resistance.
Dwg.0/9
FS CPI
FA AB; DCN
MC CPI: **A12-V01**; B01-D02; B04-E01; B10-A04; B10-B01B; B12-K04F; B14-S03; B14-S11; D05-H07; D05-H09; D05-H12E; D05-H16A; D05-H17B

L74 ANSWER 19 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1997-549493 [50] WPIX
CR 1998-427687 [36]
DNC C1997-175210
TI Polypeptide composition able to reversibly transit between **lipophilic** and **hydrophilic** forms - is useful for transporting compounds across lipid layers.
DC B04 B07
IN SUMMERTON, J E; WELLER, D D
PA (ANTI-N) ANTIVIRALS INC; (AVIB-N) AVI BIOPHARMA INC
CYC 76
PI WO 9740854 A2 19971106 (199750)* EN 73 A61K047-48 <--
RW: AT BE CH DE DK EA ES FI FR GB GH GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CZ DE DK EE ES FI GB GE GH HU IL IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK TJ TM TR TT UA UG UZ VN YU
AU 9729298 A 19971119 (199812)
EP 966303 A2 19991229 (200005) EN
R: AT BE CH DE FR GB IT LI LU NL
US 6030941 A 20000229 (200018) A01N037-18
JP 2000509394 W 20000725 (200041) 93 A61K047-48 <--
AU 729643 B 20010208 (200113) A61K047-48 <--
ADT WO 9740854 A2 WO 1997-US7335 19970430; AU 9729298 A AU 1997-29298 19970430; EP 966303 A2 EP 1997-923513 19970430, WO 1997-US7335 19970430; US 6030941 A Provisional US 1996-16347P 19960501, Provisional US 1996-28609P 19961023, US 1997-848844 19970430; JP 2000509394 W JP 1997-539221 19970430, WO 1997-US7335 19970430; AU 729643 B AU 1997-29298 19970430
FDT AU 9729298 A Based on WO 9740854; EP 966303 A2 Based on WO 9740854; JP 2000509394 W Based on WO 9740854; AU 729643 B Previous Publ. AU 9729298, Based on WO 9740854
PRAI US 1996-28609P 19961023; US 1996-16347P 19960501;

ICA C07D307-20
AB WO 9704796 A UPAB: 20040310
Compsn., comprising a therapeutic agent, coupled conjugatively, covalently,and stabilisingly with molecule(s) of a non-naturally occurring polymer (NNOP), which contains **hydrophilic** and **lipophilic** (H and L) parts and which imparts balanced H and L characteristics to the compsn., so that it is soluble in solvents and able to interact with biological membranes, is new.

USE - The conjugate is of use for admin. of a wide range of diagnostic, prophylactic, and therapeutic agents, partic. those degraded by plasma proteases when admin. parenterally, or gastrointestinal proteases on oral admin. These include proteins, enzymes, peptides, nucleosides, nucleotides, antiviral or antineoplastic agents, antibiotics, antiarrhythmics. and anticoagulants.

Most notably, the conjugate is with insulin; other examples are calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, thyroid stimulating or parathyroid hormone, erythropoietin, hypothalamic releasing factor, prolactin, endorphins, antibodies, haemoglobin, soluble CD-4, clotting factors, tissue plasminogen activator, enkephalins, vasopressin, non-natural opioids, superoxidedismutase, interferon, asparginase, arginase, arginine deaminease or adenosine deaminase ribonuclease, trypsin, chymotrypsin, papain, polypeptides, enzyme-protein or antibody-hapten conjugates, viral epitopes; antivirals are arabino-furanosyl-adenine, acylguanosine, nordeoxy-guanosine, AZT, ddA, ddC; anticancer agents are ddI, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, and L-darubicin; antibiotics are erythromycin, vancomycin, oleandomycin, and ampicillin; antiarrhythmics are quinidine; and as an anticoagulant, heparin.

Examples of diagnostic use are in screening for AIDS, hepatitis, or rubella, or other immunoassay. Both clinical and veterinary applications are envisaged.

The conjugates may also have applications in prophylaxis or treatment of plant disorders, with insecticidal, herbicidal, fungicidal, and/or pesticidal active agents.

ADVANTAGE - The conformation of the conjugate can be arranged to impart increased resistance to enzymatic degradation to the bioactive drug, notably by the **lipophilic** moiety being on the exterior, when viewed in 3-dimensional form, providing protection. Linkage of the active agent can be through a divalent spacer gp., e.g., polyethylene glycol, so as to avoid reduction of activity caused by a direct link. The polymer may also improve thermal and room temperature stability, improving shelf life and robustness of agent packs and kits. Polyalkylene glycol and polysorbate derivs., partic with M.weight in the pref. range of 500-10000 D, have no antigenic or immunogenic response, high biocompatibility, and ease of excretion.

Dwg.0/2
FS CPI
FA AB; DCN
MC CPI: A10-E07; A10-E08A; **A12-V01**; A12-V03C2; **B04-C03**; **B04-C03C**; B04-J03A; B11-C08E; B12-K04A4

L74 ANSWER 21 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1994-341060 [42] WPIX
CR 1995-274901 [36]; 1997-145369 [13]; 2001-373408 [39]; 2004-178651 [17]; 2004-178652 [17]
DNC C1994-155400
TI New peptide-polymer conjugates - containing polymer with **lipophilic** and **hydrophilic** components, especially polyethylene glycol derivative.
DC A96 B04
IN **EKWURIBE, N N**
PA (PROT-N) PROTEIN DELIVERY INC; (NOBE-N) **NOBEX CORP**
CYC 24
PI US 5359030 A 19941025 (199442)* 22 C07K007-40 <--
WO 9426778 A1 19941124 (199501) EN 76
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL PT SE
W: AU CA JP
AU 9469466 A 19941212 (199522)
EP 707596 A1 19960424 (199621) EN
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 08510255 W 19961029 (199705) 81 C07K014-00 <--
CN 1120457 A 19960417 (199745)# A61K038-22 <--
EP 707596 A4 19971112 (199840)
AU 694919 B 19980806 (199843)
IL 109619 A 20001206 (200103) A61K038-17 <--
MX 196965 B 20000615 (200133)# C07K007-040 <--
EP 1264837 A1 20021211 (200301) EN C07K001-107 <--

US 1997-848844 19970430
IC ICM A01N037-18; **A61K047-48**
ICS **A61K031-337**; **A61K031-74**; A61P001-04; A61P031-04; A61P035-00; A61P043-00
ICA A61K038-00
AB WO 9740854 A UPAB: 20010307
A new composition, for transporting a compound from a low pH environment across a lipid layer to a higher pH aqueous compartment, comprises: (a) a polypeptide (PP) containing one or more pairs of carboxyl groups; where: (i) the carboxyl groups of a pair are separated by 0, 2 or 3 amino acids; (ii) the PP has a length of 8-100 amino acid residues; (iii) the PP can undergo a reversible transition between a **lipophilic** form (which can partition from the low pH environment into the lipid layer) and a **hydrophilic** form (which can partition preferentially from the lipid layer into the higher pH compartment; and (iv) the PP contains an initiator moiety at one end region, to facilitate entry of the end region into the lipid layer; where the PP is able to traverse the lipid layer from the low-pH to the higher-pH compartment; and (b) the compound to be transported, which is covalently attached to the PP.
USE - The composition may be used for delivery of drugs across membranes (especially cell membranes or the extracellular lipid matrix of the stratum corneum) for treatment of, e.g., tumours, Helicobacter pylori infection, tooth decay (where the cell is an acid-producing cariogenic bacterial cell). The composition may be administered orally, transdermally or parenterally.
ADVANTAGE - The compositions allow more effective delivery of drugs and other compounds across lipid layers. They can deliver compounds into cells via a route which avoids exposure to lysosomal enzymes. The compositions may be prepared using known methods.
Dwg.0/14
FS CPI
FA AB; DCN
MC CPI: **B04-C01G**; B04-N04

L74 ANSWER 20 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1997-145369 [13] WPIX
CR 1994-341060 [42]; 1995-274901 [36]; 2001-373408 [39]; 2004-178651 [17]; 2004-178652 [17]
DNC C1997-046381
TI Bioactive agent conjugates with **hydrophilic** or **lipophilic** polymers - having improved stability to degradation and passage through membranes, used with proteins, peptide(s), e.g., insulin, nucleotide(s), antibiotics, etc..
DC A25 A96 B04 B07
IN **EKWURIBE, N N**
PA (PROT-N) PROTEIN DELIVERY INC
CYC 25
PI WO 9704796 A1 19970213 (199713)* EN 60 A61K038-16 <--
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU CA CN IL JP MX
AU 9666409 A 19970226 (199725)
US 5681811 A 19971028 (199749) 23 A61K037-16
EP 841936 A1 19980520 (199824) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
AU 698944 B 19981112 (199906)
JP 11511131 W 19990928 (199952) 60 A61K047-48 <--
MX 9800883 A1 19980901 (200017)
CN 1192690 A 19980909 (200040) A61K038-16 <--
MX 205730 B 20011219 (200362) A61K038-16 <--
ADT WO 9704796 A1 WO 1996-US12425 19960729; AU 9666409 A AU 1996-66409 19960729; US 5681811 A Div ex US 1993-59701 19930510, CIP of US 1994-276890 19940719, US 1995-509422 19950731; EP 841936 A1 EP 1996-926169 19960729, WO 1996-US12425 19960729; AU 698944 B AU 1996-66409 19960729; JP 11511131 W WO 1996-US12425 19960729, JP 1997-507838 19960729; MX 9800883 A1 MX 1998-883 19980130; CN 1192690 A CN 1996-196079 19960729; MX 205730 B WO 1996-US12425 19960729, MX 1998-883 19980130
FDT AU 9666409 A Based on WO 9704796; US 5681811 A Div ex US 5359030, CIP of US 5438040; EP 841936 A1 Based on WO 9704796; AU 698944 B Previous Publ. AU 9666409, Based on WO 9704796; JP 11511131 W Based on WO 9704796
PRAI US 1995-509422 19950731; US 1993-59701 19930510; US 1994-276890 19940719
REP US 4003792; US 4179337; US 4585754
IC ICM A61K037-16; **A61K038-16**; **A61K047-48**
ICS **A61K031-47**; **A61K031-52**; **A61K031-55**; **A61K031-70**; **A61K031-715**; **A61K038-00**; **A61K038-28**; A61K049-00; C08L059-00

DE 69325279 E 19990715 (199934) C07K007-06 <--
ES 2136130 T3 19991116 (200001) C07K007-06 <--
ADT WO 9406450 A1 WO 1993-US9057 19930917; AU 9351379 A AU 1993-51379 19930917; EP 661986 A1 EP 1993-922358 19930917, WO 1993-US9057 19930917; US 5624894 A Cont of US 1992-946062 19920917, US 1995-428488 19950427; EP 661986 A4 EP 1993-922358 ; AU 694094 B AU 1993-51379 19930917; EP 661986 B1 EP 1993-922358 19930917, WO 1993-US9057 19930917; DE 69325279 E DE 1993-625279 19930917, EP 1993-922358 19930917, WO 1993-US9057 19930917; ES 2136130 T3 EP 1993-922358 19930917
FDT AU 9351379 A Based on WO 9406450; EP 661986 A1 Based on WO 9406450; AU 694094 B Previous Publ. AU 9351379, Based on WO 9406450; EP 661986 B1 Based on WO 9406450; DE 69325279 E Based on EP 661986, Based on WO 9406450; ES 2136130 T3 Based on EP 661986
PRAI US 1992-946062 19920917; US 1995-428488 19950427
REP US 4888427; US 4829070
IC ICM A61K037-00; **A61K038-03**; **C07K005-02**; **C07K007-06**
ICS **A61K038-02**; **A61K047-48**; **C07K005-08**; **C07K005-10**; **C07K007-02**; **C07K014-70**
AB WO 9406450 A UPAB: 19981021
Dihydropyridine substd. peptides of formula (I), and their pharmaceutically acceptable salts, and the corresponding pyridinium salts (II) are new. In the formula, Z = direct bond or 1-6C alkylene, attached to ring C or N; R1 = 1-7C (halo)alkyl or 7-12C aralkyl when Z is attached to C or a bond when Z is attached to N; R2 and R3 = H, halo, CN, 1-7C alkyl, alkoxy or alkyl S(O)n (n=0-2), 2-8C alkoxycarbonyl or alkanoyloxy, 1-7C haloalkyl, CH=NOR''' or CONR'R''; R',R'' and R''' = H or 1-7C alkyl; one of R2 and R3, together with an adjacent ring C may form a fused benzene ring, opt. substd. by 1 or 2 substits. as defined for R2 and R3, or opt. protected OH; the dotted lines indicate 1,4- or 1,6-dihydropyridine, 1,4- or 1,2-dihydroquinoline or 1,2-dihydroisoquinoline; spacer indicates 1-3L amino acid residues, the N-terminal one being bonded to CO; peptide indicates a pharmacologically active peptide of 2-20 amino acids, the N-terminal one being bonded to the C terminus of spacer, and the C-terminal one having esterified function COOR4; R4 = 5-22C alkyl or alkenyl, or 6-30C polycycloalkyl-CpH2p or polycycloalkenyl-CpH2p; p = 0-3; X = anion of nontoxic, pharmaceutically acceptable acid.
USE - (I) are used for site specific and/or sustained delivery of active peptides to the brain. Because they are **lipophilic** they can cross the blood-brain barrier, but once in the brain they are oxidised to **hydrophilic** (II) which is unable to leave the brain. Brain enzymes then degrade (II), releasing the active peptide. (II) are also intermediates in synthesis of (I). Pref. peptides are the analgesic kyotrphin (Tyr-Arg) which stimulates release of enkephalins; thyrotropin-releasing hormone or its analogues, or Met5- and Leu5-enkephalins or their analogues which are analgesics and affect memory so can be used to treat e.g. Alzheimer's disease).
Dwg.1/5
FS CPI
FA AB; GI; DCN
MC CPI: **B04-C01**; B04-N02; B06-D02; B06-D03; B07-D04A; B07-D04C

=> b hcap

FILE 'HCAPLUS' ENTERED AT 12:23:51 ON 13 OCT 2004
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

FILE COVERS 1907 - 13 Oct 2004 VOL 141 ISS 16
FILE LAST UPDATED: 12 Oct 2004 (20041012/ED)

This file contains CAS Registry Numbers for easy and accurate

R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
JP 2003160598 A 20030603 (200346) 27 C07K014-62 <--
JP 2003206236 A 20030722 (200351) 32 A61K038-00 <--
ADT US 5359030 A US 1993-59701 19930510; WO 9426778 A1 WO 1994-US5204 19940510; AU 9469466 A AU 1994-69466 19940510; EP 707596 A1 EP 1994-917946 19940510, WO 1994-US5204 19940510; JP 08510255 W JP 1994-525657 19940510, WO 1994-US5204 19940510; CN 1120457 A CN 1994-117233 19941014; EP 707596 A4 EP 1994-917946 19940510; AU 694919 B AU 1994-69466 19940510; IL 109619 A IL 1994-109619 19940511; MX 196965 B MX 1994-7611 19940930; EP 1264837 A1 Div ex EP 1994-917946 19940510, EP 2002-77075 19940510; JP 2003160598 A Div ex JP 1994-525657 19940510, JP 2002-260459 19940510; JP 2003206236 A Div ex JP 1994-525657 19940510, JP 2002-260460 19940510
FDT AU 9469466 A Based on WO 9426778; EP 707596 A1 Based on WO 9426778; JP 08510255 W Based on WO 9426778; AU 694919 B Previous Publ. AU 9469466, Based on WO 9426778; EP 1264837 A1 Div ex EP 707596
PRAI US 1993-59701 19930510; CN 1994-117233 19941014;
MX 1994-7611 19940930
REP 02Jnl.Ref; US 4044196; US 4849405; US 5013556; 1.Jnl.Ref; EP 354855; EP 92918; US 4179337; US 5108568
IC ICM **A61K038-00**; **A61K038-17**; **A61K038-22**; **C07K001-107**; **C07K007-040**; **C07K007-40**; **C07K014-00**; **C07K014-62**
ICS **A61K038-02**; **A61K038-04**; **A61K038-11**; **A61K038-21**; **A61K038-23**; **A61K038-26**; **A61K038-27**; **A61K038-28**; **A61K038-35**; **A61K038-43**; **A61K038-44**; **A61K038-46**; **A61K038-48**; A61K047-34; **A61K047-48**; A61P003-10; A61P005-50; **C07K007-036**; **C07K007-36**; **C07K017-008**; **C07K017-02**; **C07K017-08**; C08G065-26; C08G069-10; C08G069-40; C08G081-02; C08H001-00; C08H001-000; C08L071-02
AB US 5359030 A UPAB: 20040310
New conjugates comprise: (a) a peptide (I) covalently coupled to one or more mols. of a non-natural polymer having **lipophilic** and **hydrophilic** polymer components, where the conjugate is soluble in pharmaceutically acceptable solvents and is able to interact with biological membranes.

Pref. conjugate (II) comprises a physiologically active peptide covalently coupled to one or more mols. of a polymer comprising a linear polyalkylene glycol component and a **lipophilic** component arranged so as to enhance the resistance of the peptide to enzymatic degradation in vivo; the peptide is soluble in aqueous solvents and is active against plant disorders.

USE - The conjugates may be used for therapeutic or diagnostic purposes.

ADVANTAGE - The conjugates have improved properties compared with the free peptide, e.g. better epithelial penetration, resistance to proteolytic degradation, affinity for endogenous transport systems and/or resistance to stomach acidity.

Dwg.0/2
FS CPI
FA AB; GI; DCN
MC CPI: **A12-V01**; A12-V03C2; **B04-C01**; **B04-C03C**; B12-K04; B14-E01

L74 ANSWER 22 OF 22 WPIX COPYRIGHT 2004 THE THOMSON CORP on STN
AN 1994-118149 [14] WPIX
DNC C1994-054638
TI New peptide derivs. with di hydro pyridine redox gp. - for site specific and sustained drug delivery to the brain.
DC B04
IN BODOR, N S
PA (UYFL) UNIV FLORIDA
CYC 46
PI WO 9406450 A1 19940331 (199414)* EN 271 A61K037-00
RW: AT BE CH DE DK ES FR GB GR IE IT LU MC NL OA PT SE
W: AT AU BB BG BR BY CA CH CZ DE DK ES FI GB HU JP KP KR KZ LK LU LV MG MN MW NL NO NZ PL PT RO RU SD SE SK UA VN
AU 9351379 A 19940412 (199431) A61K037-00
EP 661986 A1 19950712 (199532) EN A61K037-00
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE
US 5624894 A 19970429 (199723) 101 A61K038-03 <--
EP 661986 A4 19970423 (199735) A61K037-00
AU 694094 B 19980716 (199840) C07K005-02 <--
EP 661986 B1 19990609 (199927) EN C07K007-06 <--
R: AT BE CH DE DK ES FR GB GR IE IT LI LU MC NL PT SE

substance identification.

=> d all l64 tot

L64 ANSWER 1 OF 1 HCAPLUS COPYRIGHT 2004 ACS on STN
AN 2001:131193 HCAPLUS
DN 134:183490
ED Entered STN: 22 Feb 2001
TI Hydrophilic and lipophilic balanced microemulsion formulations of free-form and/or conjugation-stabilized therapeutic agents such as insulin
IN **Ekwuribe, Nnochiri Nkem**; Ramaswamy, Muthukumar; **Radhakrishnan, Balasingam**; Allaudeen, Hameedsulthan S.
PA **Protein Delivery, Inc., USA**
SO U.S., 32 pp., Cont.-in-part of U. S. 5,681,811.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K038-38
ICS C07K014-62
NCL 514003000
CC 63-6 (Pharmaceuticals)
Section cross-reference(s): 1, 2
FAN.CNT 4

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 6191105	B1	20010220	US 1997-958383	19971027
	US 5359030	A	19941025	US 1993-59701	19930510
	US 5438040	A	19950801	US 1994-276890	19940719
	US 5681811	A	19971028	US 1995-509422	19950731
	US 2003229006	A1	20031211	US 2003-448524	20030530
	US 2003229010	A1	20031211	US 2003-448535	20030602
PRAI	US 1993-59701	A3	19930510		
	US 1994-276890	A2	19940719		
	US 1995-509422	A2	19950731		
	US 1997-958383	A3	19971027		
	US 2000-614203	A1	20000712		

CLASS

PATENT NO.	CLASS	PATENT FAMILY CLASSIFICATION CODES
US 6191105	ICM	A61K038-38
	ICS	C07K014-62
	NCL	514003000
US 5359030	ECLA	A61K009/107D; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62; C12N009/96
US 5438040	ECLA	A61K009/107D; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62; C12N009/96
US 5681811	ECLA	A61K009/107D; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62
US 2003229006	ECLA	A61K009/107D; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K014/62; A61K038/28; A61K038/46; A61K047/4H4P; C12N009/96
US 2003229010	ECLA	A61K009/107D; A61K038/28; A61K038/46; A61K047/48H4P; A61K047/48K; A61K049/00P4F; C07K001/107D4; C07K001/62; C12N009/96

AB A therapeutic formulation comprising a microemulsion of a therapeutic agent in free and/or conjugate coupled form, wherein the microemulsion comprises a water-in-oil (w/o) microemulsion including a lipophilic phase and a hydrophilic phase, and has a hydrophilic and lipophilic balance (HLB) value between 3 and 7 is described. The therapeutic agent is selected from the group consisting of insulin, calcitonin, ACTH, glucagon, somatostatin, somatotropin, somatomedin, parathyroid hormone, erythropoietin, hypothalamic releasing factors, prolactin, thyroid stimulating hormones, endorphins, enkephalins, vasopressin, non-naturally occurring opioids, superoxide dismutase, interferon, asparaginase, arginase, arginine deaminease, adenosine deaminase, RNase, trypsin, chymotrypsin, papain, Ara-A (Arabinofuranosyladenine), acylguanosine, nordeoxyguanosine, azidothymidine, dideoxyadenosine, dideoxycytidine, dideoxyinosine, floxuridine, 6-mercaptopurine, doxorubicin, daunorubicin, or I-darubicin, erythromycin, vancomycin, oleandomycin, ampicillin, quinidine and heparin. In a particular aspect, the invention comprises an insulin composition suitable for parenteral as well as non-parenteral administration, preferably oral or parenteral administration, comprising insulin covalently coupled with a polymer including (i) a linear polyalkylene glycol moiety and (ii) a lipophilic moiety, wherein the insulin, the linear polyalkylene glycol moiety and the lipophilic moiety

are conformationally arranged in relation to one another such that the insulin in the composition has an enhanced in vivo resistance to enzymic degradation, relative to insulin alone. The microemulsion compns. of the invention are usefully employed in therapeutic as well as non-therapeutic, e.g., diagnostic, applications. For example, a microemulsion formulation was prepared containing Capmul MCM 53.0, Centrophase 31 5.7, propylene glycol 19.9, Tween 80 1.4, hexyl insulin in NaP buffer 15 mg/mL, and NaP buffer up to 100%, resp. Also, preparation of hexyl insulin conjugates with Me (ethylene glycol)7-O-hexanoic acid was carried out.

ST drug conjugate microemulsion stabilization; insulin conjugate microemulsion stabilization

IT Fatty acids, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(C8-10, esters with propylene glycol; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Diagnosis
(agents; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Polyoxyalkylenes, biological studies
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(conjugates with tetrahydropyran derivative and insulin; hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT **Antidiabetic agents**
Hydrophile-lipophile balance value
(hydrophilic and lipophilic balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Diglycerides
Enkephalins
Glycerides, biological studies
Hypothalamic hormones
Interferons
Lecithins
Monoglycerides
Opioids
Polymers, biological studies
Polyoxyalkylenes, biological studies
Polyoxyalkylenes, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Drug delivery systems
(microemulsions; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Surfactants
(nonionic; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Drug delivery systems
(oral; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Drug delivery systems
(parenterals; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Alcohols, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(polyhydric; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT Fats and Glyceridic oils, biological studies
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(vegetable; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 24167-76-8, Sodium phosphide
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(buffer; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 102-82-9, Tri-n-butylamine 3344-77-2, 12-Bromo-1-dodecanol 7075-11-8 7693-46-1, p-Nitrophenylchloroformate 9004-74-4 9005-66-7 9005-70-3 11070-73-8, Bovine insulin 25512-65-6, Dihydropyran 161489-28-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 7075-11-8DP, tri-Bu derivative 88517-92-4P 100601-63-6P 161756-38-3P 161756-39-4P 212969-35-2P 326892-08-4P 326892-09-5P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 9004-95-9DP, Polyoxyethylene cetyl ether, conjugates with tri-Bu AraCMP 9004-99-3DP, Polyethylene glycol monostearate, conjugates with insulin 9005-66-7DP, conjugates with insulin 9005-70-3DP, conjugates with polysorbate trioleate 11070-73-8DP, Bovine insulin, conjugates 25322-68-3DP, Polyethylene glycol, conjugates with tetrahydropyran derivative and insulin 88517-92-4DP, conjugates with insulin and polyethylene glycol 212969-35-2DP, conjugates with hexyl insulin
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 50-44-2, 6-Mercaptopurine 50-91-9, Floxuridine 56-54-2, Quinidine 57-55-6, Propylene glycol, biological studies 57-55-6D, Propylene glycol, esters **69-53-4**, Ampicillin 69-65-8, D-Mannitol 114-07-8, Erythromycin 118-00-3D, Guanosine, acyl derivs., biological studies **1404-90-6**, Vancomycin 1984-06-1, Sodium octanoate 3922-90-5, Oleandomycin 4097-22-7, Dideoxyadenosine 5536-17-4, Ara-A 7481-89-2, Dideoxycytidine 9000-96-8, Arginase 9001-73-4, Papain 9001-99-4, RNase 9002-07-7, Trypsin 9002-60-2, ACTH, biological studies 9002-62-4, Prolactin, biological studies 9002-64-6, Parathyroid hormone 9002-71-5, Thyroid stimulating hormone 9002-72-6, Somatotropin 9004-07-3, Chymotrypsin 9004-10-8, Insulin, biological studies 9004-10-8D, Insulin, conjugates with hexanoic acid derivative, biological studies 9004-10-8D, Insulin, hexyl polymer conjugate, biological studies 9005-49-6, Heparin, biological studies 9005-65-6, Tween 80 9007-12-9, Calcitonin **9007-92-5**, Glucagon, biological studies 9015-68-3, Asparaginase 9026-93-1, Adenosine deaminase 9027-98-9 9038-70-4, Somatomedin 9054-89-1, Superoxide dismutase **11000-17-2**, Vasopressin 11096-26-7, Erythropoietin **20830-81-3**, Daunorubicin 23214-92-8, Doxorubicin 25322-68-3, Polyethylene glycol 30516-87-1, Azidothymidine **51110-01-1**, Somatostatin 58957-92-9, I-Darubicin **60118-07-2**, Endorphin 69655-05-6, Dideoxyinosine 82410-32-0 87090-08-2, Labrafil M 1944 120300-18-7, Caprol PGE 860 156259-68-6, Capmul MCM 195739-92-5, Centrophase 31
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin)

IT 9001-92-7, Protease
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; **hydrophilic** and **lipophilic** balanced microemulsions of free and/or conjugated drugs such as insulin but nor protease inhibitor)

IT 8049-47-6, Pancreatin 9001-75-6, Pepsin
RL: CAT (Catalyst use); USES (Uses)
(insulin and its conjugates stability in)

RE.CNT 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L73 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1985:589177** HCAPLUS
DN 103:189177
ED Entered STN: 14 Dec 1985
TI Plasma and tear concentrations of antibiotics administered parenterally to cattle
AU Punch, P. I.; Costa, N. D.; Chambers, E. D.; Slatter, D. H.; Wilcox, G. E.
CS Sch. Vet. Stud., Murdoch Univ., Murdoch, 6150, Australia
SO Research in Veterinary Science (**1985**), 39(2), 179-87
CODEN: RVTSA9; ISSN: 0034-5288
DT Journal
LA English
CC 1-2 (Pharmacology)
AB Chloramphenicol [56-75-7], erythromycin [114-07-8], gentamicin [**1403-66-3**], oxytetracycline [**79-57-2**], penethamate [3689-73-4], and procaine benzylpenicillin [6130-64-9] were administered parenterally to cattle and the concns. of these antibiotics in plasma and tears were assayed microbiol. Concns. in plasma and tears were correlated for all antibiotics tested but the concentration of antibiotic in tears and the tear flow rate were not correlated. **Lipophilic** drugs diffused into the tears in higher concns. than did drugs which were not **lipophilic.** Concns. of **lipophilic** but not **hydrophilic** antibiotics in tears could be predicted from the Henderson-Hasselbach equation. In cattle, it is possible through parenteral administration of chloramphenicol, erythromycin, gentamicin, or oxytetracycline to achieve antibiotic concns. in the tears which are bacteriostatic to Moraxella bovis, a primary etiol. agent of infectious bovine keratoconjunctivitis.
ST plasma tear antibiotic cattle
IT Cattle
(antibiotics levels in plasma and tears in, correlation of, keratoconjunctivitis from Moraxella bovis treatment in relation to)
IT Tear
(antibiotics of, levels in plasma correlation with, in cattle)
IT Blood plasma
(antibiotics of, levels in tears correlation with, in cattle)
IT Moraxella bovis
(keratoconjunctivitis from, in cattle, treatment of, antibiotic levels in plasma and tears in relation to)

IT Lipophilicity
(of antibiotics, transport into tears in cattle in relation to)
IT **Antibiotics**
(of plasma and tears, correlation of, in cattle)
IT Eye, disease or disorder
(keratoconjunctivitis, from Moraxella bovis, treatment of, antibiotic levels in plasma and tears of cattle in relation to)
IT 56-75-7 **79-57-2** 114-07-8 **1403-66-3** 3689-73-4
6130-64-9
RL: BIOL (Biological study)
(of plasma and tears, correlation of, in cattle)

L73 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1982:593254** HCAPLUS
DN 97:193254
ED Entered STN: 12 May 1984
TI Critical components of opioid peptides for specific recognition of .mu. and .delta. receptors
AU Gacel, G.; Fournie-Zaluski, M. C.; David, M.; Meunier, J. C.; Morgat, J. L.; Roques, B. P.
CS Dep. Chim. Org., CNRS, Paris, 75006, Fr.
SO Adv. Endog. Exog. Opioids, Proc. Int. Narc. Res. Conf., 12th (**1981**), 377-9. Editor(s): Takagi, Hiroshi; Simon, Eric J. Publisher: Kodansha, Tokyo, Japan.
CODEN: 48NVAY
DT Conference
LA English
CC 2-2 (Mammalian Hormones)
AB Of the 13 opioid peptides tested for binding in the guinea pig ileum and mouse vas deferens, Tyr-L-Ser-Gly-Phe-Leu-Thr (DSTLE) [75644-90-5] and Tyr-D-Ala-Gly-NHCH(CH3)CH2 (TRIMU 4) [72732-17-3] were the most selective probes for use in the characterization of .delta. and .mu. receptor subtypes, resp. DSTLE labeled only .delta. sites in rat brain homogenates, whereas Tyr-D-Ala-Gly-Phe-D-Leu [**63631-40-3**] bound both .mu. and .delta. receptor subtypes and TRIMU 4 preferentially labeled .mu.-sites. Substitution with 2-D-amino acids, shortening the enkephalin sequence, removal of the 4-phenylalanine residue, and addition of a C-terminal alkyl **lipophilic** chain enhanced the .mu.-receptor specificity of the enkephalins, whereas lengthening the enkephalin chain, introduction of a 5-leucine residue, and insertion of an **hydrophilic** residue, such as D-serine, in position 2 enhanced the .delta.-receptor specificity of the enkephalins.
ST enkephalin receptor structure activity; opioid activity enkephalin analog
IT Brain, metabolism
(enkephalin analog binding by, structure in relation to)
IT **Enkephalins**
RL: PROC (Process)
(opiate receptor binding of, structure in relation to)
IT Molecular structure-biological activity relationship
(opiate receptor-binding, of enkephalin analogs)
IT **Receptors**
RL: BIOL (Biological study)
(.delta.-, enkephalin binding by, structure in relation to)
IT **Receptors**
RL: BIOL (Biological study)
(.mu.-, enkephalin binding by, structure in relation to)
IT **58569-55-4** **58822-25-6** 60117-18-2 **63631-40-3**
64854-64-4 66609-07-2 72732-16-2 72732-17-3 72732-18-4
75644-90-5 80638-47-7 80648-16-4 83329-17-3
RL: PROC (Process)
(opiate receptor binding of, structure in relation to)

L73 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1982:63137** HCAPLUS
DN 96:63137
ED Entered STN: 12 May 1984
TI Structural requirements for specific recognition of .mu. or .delta. opiate receptors
AU Fournie-Zaluski, Marie Claude; Gacel, Gilles; Maigret, Bernard; Premilat, Samuel; Roques, Bernard P.
CS Dep. Chim. Org., CNRS, Paris, 75006, Fr.
SO Molecular Pharmacology (**1981**), 20(3), 484-91
CODEN: MOPMA3; ISSN: 0026-895X
DT Journal
LA English
CC 2-2 (Mammalian Hormones)

AB A comparison of the inhibitory potency of new analogs of enkephalins on the evoked contractions of guinea pig ileum (.mu. receptors) and mouse vas deferens (.delta. receptors) allows the definition of the structural components required for specific recognition of .mu. or .delta. receptors. A high specificity for .mu. binding sites is obtained by shortening the enkephalin sequence and removing the terminal carboxyl group, by replacing the aromatic Phe4 residue with a **lipophilic** alkyl chain, and by introducing as a 2nd residue a hydrophobic amino acid of the D-configuration whose side-chain probably interacts with a specific .mu.-receptor subsite. Compared with methionine-enkephalin [**58569-55-4**] such modifications lead to a 99% loss of potency on mouse vas deferens but a 2-fold enhanced activity on guinea pig ileum. These short peptides display a high folding tendency. The low-energy conformer of the highest .mu.-specific peptide exhibits a T-shaped structure similar to that of morphine. All of the proposed .mu.-specific requirements account for the reported variations in the biol. activity of various modified enkephalins. The .mu.-agonist potency of endogenous enkephalins was related to a fitting of the side-chain of their 5th amino acid in the .mu. hydrophobic subsite. The requirements for .delta. receptor specificity are even more strict and involve an aromatic moiety in the 4th position, a conformational key role of the amino acid(s) following the Phe4, improving the fitting of the Phe4 side-chain in a specific .delta.-receptor subsite, and a lengthening of the enkephalin sequence and the introduction of a **hydrophilic** side-chain in position 2 which decrease the .mu. specificity. These modifications lead to peptides almost 3 orders of magnitude more active on mouse vas deferens than on guinea pig ileum. .mu. Receptors bind preferentially highly hydrophobic compds. with compact structures, whereas .delta. receptors exhibit a stronger affinity for larger peptides with **hydrophilic** components. Thus 3H-labeled Tyr-D-Ser-Gly-Phe-Leu-Thr, the most selective .delta. agonist, interacts exclusively with .delta.-binding sites at concns. up to 20 nM. In contrast, Tyr-D-Ala-Gly-NH-CH(CH3)-CH2-CH(CH3)2 exhibits a specificity almost 50 times greater for .mu. receptors than for .delta. receptors.

ST enkephalin analog opiate receptor; conformation peptide opiate receptor

IT **Enkephalins**
RL: BIOL (Biological study)
(analogs, opiate activity of, structure in relation to)

IT **Receptors**
RL: BIOL (Biological study)
(for opiates, enkephalin analogs binding by, structural requirements for)

IT Conformation and Conformers
(of enkephalin analogs, opiate receptors binding in relation to)

IT **Receptors**
RL: BIOL (Biological study)
(.sigma.-, enkephalins binding by, structural requirements for)

IT Molecular structure-biological activity relationship
(opiate receptor-binding, of enkephalin analogs)

IT **Receptors**
RL: BIOL (Biological study)
(.mu.-, enkephalins binding by, structural requirements for)

IT **58569-55-4**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(opiate activity of, enkephalin analogs in relation to)

IT 57-27-2, biological studies **58569-55-4 58822-25-6**
60117-18-2 61370-87-4 **63631-40-3** 64963-01-5 66609-07-2
66649-46-5 67706-17-6 68905-83-9 72732-16-2 72732-17-3
72732-18-4 75644-90-5 80638-46-6 80638-47-7 80648-16-4
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(opiate activity of, structure in relation to)

L73 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN
AN **1976:22038** HCAPLUS
DN 84:22038
ED Entered STN: 12 May 1984
TI Characteristics of ambiphile salves and cream foundations
AU Nuernberg, Eberhard
CS Inst. Pharm. Technol., Fa. E. Merck, Darmstadt, Fed. Rep. Ger.
SO Pharmazeutische Zeitung (**1975**), 120(39), 1509-19
CODEN: PHZIAP; ISSN: 0031-7136
DT Journal
LA German
CC 63-5 (Pharmaceuticals)

AB The elec. conductivity, isothermal moisture evaporation, and agar diffusion behavior of **hydrophilic**, **lipophilic**, and ambiphilic cream bases, and their in vitro release of salicylic acid [69-72-7] and gentamycin sulfate [**1405-41-0**] were studied. In spite of their lower **hydrophilicity**, the ambiphilic cream bases showed release properties which were as favorable or even more favorable than those of an oil-in-water system.
ST cream ambiphile release property
IT Cosmetics
Pharmaceuticals
(ambiphilic cream foundations for, properties of)
IT Ointments
(ambiphilic, properties of)
IT 69-72-7, properties **1405-41-0**
RL: PRP (Properties)
(release of, by ambiphilic creams)

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This file contains CAS Registry Numbers for easy and accurate substance identification.

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L89 ANSWER 1 OF 1 EMBASE
on STN
AN **1998275834** EMBASE
TI A system for the brain-enhanced delivery of estradiol: An assessment of its potential for the treatment of Alzheimer's disease and stroke.
AU Simpkins J.W.; Rabbani O.; Shi J.; Panickar K.S.; Green P.S.; Day A.L.
CS Dr. J.W. Simpkins, College of Pharmacy, University of Florida, Gainesville, FL 32610, United States
SO Pharmazie, (1998) 53/8 (505-511).
Refs: 88
ISSN: 0031-7144 CODEN: PHARAT
CY Germany
DT Journal; General Review
FS 008 Neurology and Neurosurgery
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LA English
CT Medical Descriptors:
*alzheimer disease
*stroke
*brain
*drug delivery system
cholinergic nerve cell
lipophilicity
blood brain barrier
hydrophilicity
lipid solubility
hydrolysis
oxidation reduction reaction
enzyme activity
neuroprotection
membrane depolarization
calcium homeostasis
human
nonhuman
review
Drug Descriptors:
*estradiol: AN, drug analysis
*estradiol: PK, pharmacokinetics
*estradiol: PD, pharmacology
*dihydropyridine
*pyridinium derivative
*3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridine 3 yl)carbonyl]oxy]estra 1,3,5 (10) triene: AN, drug analysis

*1 methyl 3 [[(3 hydroxyestra 1,3,5 (10) triene 17beta
yl)oxy]carbonyl]pyridinium iodide: AN, drug analysis
thromboxane: EC, endogenous compound
lipid: EC, endogenous compound
glucose: EC, endogenous compound
oxygen: EC, endogenous compound
excitatory amino acid: TO, drug toxicity
choline acetyltransferase: EC, endogenous compound
choline: EC, endogenous compound
calcium: EC, endogenous compound
cyclic amp responsive element binding protein: EC, endogenous compound
messenger rna: EC, endogenous compound
neurotrophin receptor: EC, endogenous compound
neurotrophin: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound
nerve growth factor: EC, endogenous compound
amyloid beta protein: TO, drug toxicity
glutamic acid: TO, drug toxicity
buthionine sulfoximine: TO, drug toxicity
hydrogen peroxide: TO, drug toxicity
glucose transporter: EC, endogenous compound
diethylstilbestrol
neurotransmitter: EC, endogenous compound
unclassified drug

RN (estradiol) 50-28-2; (dihydropyridine) 27790-75-6; (thromboxane) 66719-58-2; (lipid) 66455-18-3; (glucose) 50-99-7, 84778-64-3; (oxygen) 7782-44-7; (choline acetyltransferase) 9012-78-6; (choline) 123-41-1, 13232-47-8, 1927-06-6, 4858-96-2, 62-49-7, 67-48-1; (calcium) 7440-70-2; (cyclic amp responsive element binding protein) 130428-87-4, 130939-96-7; (mitogen activated protein kinase) 142243-02-5; (nerve growth factor) 9061-61-4; (amyloid beta protein) 109770-29-8; (glutamic acid) 11070-68-1, 138-15-8, 56-86-0, 6899-05-4; (buthionine sulfoximine) 5072-26-4; (hydrogen peroxide) 7722-84-1; (diethylstilbestrol) 30498-85-2, 56-53-1

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L93 ANSWER 1 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 1998344063 EMBASE
TI Mechanism of action of chromogranin A on catecholamine release: Molecular modeling of the catestatin region reveals a .beta.-strand/loop/.beta.-strand structure secured by hydrophobic interactions and predictive of activity.
AU Tsigelny I.; Mahata S.K.; Taupenot L.; Preece N.E.; Mahata M.; Khan I.; Parmer R.J.; O'Connor D.T.
CS D.T. O'Connor, Department of Medicine, Center for Molecular Genetics, University of California, San Diego, CA, United States. doconnor@ucsd.edu
SO Regulatory Peptides, (1998) 77/1-3 (43-53).
Refs: 37
ISSN: 0167-0115 CODEN: REPPDY
PUI S 0167-0115(98)00040-8
CY Netherlands
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB A novel fragment of chromogranin A, known as 'catestatin' (bovine chromogranin A344-364), inhibits catecholamine release from chromaffin cells and noradrenergic neurons by acting as a non-competitive nicotinic cholinergic antagonist, and may therefore constitute an endogenous autocrine feedback regulator of sympathoadrenal activity. To characterize how this activity depends on the peptide's structure, we searched for common 3-dimensional motifs for this primary structure or its homologs. Catestatin's primary structure bore significant (29-35.5% identity, general alignment score 44-57) sequence homology to fragment sequences within three homologs of known 3-dimensional structures, based on solved X-ray crystals: 8FAB, 1PKM, and 2IG2. Each of these sequences exists in nature as a .beta.-strand/loop/.beta.-strand structure, stabilized by hydrophobic interactions between the .beta.-strands. The catestatin structure was stable during molecular dynamics simulations. The catestatin loop contains three Arg residues, whose electropositive side chains form the terminus of the structure, and give rise to substantial uncompensated charge asymmetry in the molecule. A hydrophobic moment plot revealed that catestatin is the only segment of chromogranin A predicted to contain **amphiphilic** .beta.-strand. Circular dichroism in the far

ultraviolet showed substantial (63%) .beta.-sheet structure, especially in a hydrophobic environment. Alanine-substitution mutants of catestatin established a crucial role for the three central arginine residues in the loop (Arg351, Arg353, and Arg358), though not for two arginine residues in the strand region toward the amino-terminus. [125I]Catestatin bound to Torpedo membranes at a site other than the nicotinic agonist binding site. When the catestatin structure was 'docked' with the extracellular domain of the Torpedo nicotinic cholinergic receptor, it interacted principally with the .beta. and .delta. subunits, in a relatively hydrophobic region of the cation pore extracellular orifice, and the complex of ligand and receptor largely occluded the cation pore, providing a structural basis for the non-competitive nicotinic cholinergic antagonist properties of the peptide. We conclude that a homology model of catestatin correctly predicts actual features of the peptide, both physical and biological. The model suggests particular spatial and charge features of the peptide which may serve as starting points in the development of non-peptide mimetics of this endogenous nicotinic cholinergic antagonist. Copyright (C) 1998 Elsevier Science B.V.

CT Medical Descriptors:
*catecholamine release
*molecular model
protein structure
chromaffin granule
chromaffin cell
molecular dynamics
circular dichroism
membrane binding
article
priority journal
Drug Descriptors:
*chromogranin a: EC, endogenous compound
catestatin: EC, endogenous compound
nicotinic receptor: EC, endogenous compound
catecholamine: EC, endogenous compound
unclassified drug

L93 ANSWER 2 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 97297410 EMBASE
DN 1997297410
TI Molecular simulation of dynorphin A-(1-10) binding to extracellular loop 2 of the .kappa.-opiod receptor. A model for receptor activation.
AU Paterlini G.; Portoghese P.S.; Ferguson D.M.
CS G. Paterlini, DMCMSI, University of Minnesota, Minneapolis, MN 55455, United States
SO Journal of Medicinal Chemistry, (1997) 40/20 (3254-3262).
Refs: 58
ISSN: 0022-2623 CODEN: JMCMAR
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The structure of the second extracellular loop region (EL2) of the .kappa.- opioid receptor has been explored in an effort to understand the structural basis for dynorphin A binding and selectivity. Application of secondary structure prediction methods and homology modeling resulted in a turn-helix motif for the N-terminal region of .kappa.-EL2. A similar motif was not predicted for EL2 of either the .delta. or .mu. opioid receptors. The EL2 helix was further shown to be **amphiphilic** and complementary to the helical component of dynorphin A. Using a model of the .kappa.-receptor (Metzger et al. Neurochem. Res. 1996, 21, 1287-1294), including the newly predicted EL2 turn-helix domain, a binding mode is proposed based on helix-helix interactions between hydrophobic residues of EL2 and the helical component of dynorphin A-(1-10). Molecular simulations of the receptor-ligand complex yielded structures in which the tyramine moiety or opioid 'message' of dynorphin is bound within a conserved aromatic pocket in the transmembrane domain while the helical portion contacted residues in EL2 and in the extracellular end of transmembrane helices 6 and 7. The model is in general agreement with site- directed mutagenesis data and chimera studies that have identified binding domains in both the EL2 and transmembrane regions to dynorphin A. The results confirm the importance of the opioid 'message' displayed by many opioid ligands but also suggest a potential mechanism of receptor activation that may be mediated by EL2 through interactions with the 'address' component

of dynorphin A.
CT Medical Descriptors:
*drug receptor binding
article
drug structure
molecular model
protein secondary structure
site directed mutagenesis
Drug Descriptors:
*dynorphin a derivative: AN, drug analysis
*dynorphin a derivative: PD, pharmacology
*dynorphin[1-10]: AN, drug analysis
*dynorphin[1-10]: PD, pharmacology
***kappa opiate receptor**
unclassified drug
RN (dynorphin[1-10]) 79994-24-4

L93 ANSWER 3 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 96172594 EMBASE
DN 1996172594
TI 2-Alkyl-substituted histamines and hydroxyethylimidazoles with G-protein-stimulatory activity.
AU Detert H.; Leschke C.; Togel W.; Seifert R.; Schunack W.
CS Institut fur Organische Chemie, Johannes Gutenberg-Universitat, Johann-Joachim-Becher-Weg 18-20,D-55099 Mainz, Germany
SO European Journal of Medicinal Chemistry, (1996) 31/5 (397-405).
ISSN: 0223-5234 CODEN: EJMCA5
CY France
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB Cationic-**amphiphilic** 2-substituted histamines activate pertussis toxin-sensitive guanine nucleotide-binding proteins (G-proteins) by a receptor-independent mechanism. From our recent studies it became apparent that lipophilicity is an important determinant for this G-protein activation, but the influence of basicity remained unknown. We prepared seven novel 2-alkyl-substituted histamines and five novel 2-alkyl-substituted hydroxyethylimidazoles and studied their effects on high-affinity guanosine triphosphate (GTP) hydrolysis in membranes of the human leukemia cell line, HL-60. 2-Octylhistamine was found to be the most effective GTPase activator among 2-substituted histamines presently available (150% stimulation above basal), and 2-tetradecylhistamine is the most potent substance in this regard (pEC50 = 5.9). Branching of the alkyl chain and the introduction of an ether group adversely affected GTPase activation. Compared to a phenyl ring, a bulky adamantyl sphere enhanced G-protein-stimulatory activity. In the case of 2-(3-bromophenyl)histamine, 2-adamantylhistamine and 2-(3-phenylpropyl)histamine, replacement of the aminoethyl group by a hydroxyethyl group at the imidazole greatly reduced GTPase-activating properties, pointing to the importance of the basic domain in the activation process. Unexpectedly, however, in the case of a very lipophilic substituent (heptadecyl chain) the exchange of the aminoethyl group by a hydroxyethyl group had no substantial inhibitory effect, indicating that the presence of a primary amine is not a conditio sine qua non for a substance being a receptor-independent G-protein activator. Concerning histamine H1-receptors the newly prepared compounds proved to be weak antagonists.
CT Medical Descriptors:
*cell membrane
*enzyme activation
animal tissue
article
controlled study
drug receptor binding
drug synthesis
guinea pig
human
human cell
ileum
leukemia cell line
lipophilicity
nonhuman
structure activity relation

Drug Descriptors:
*guanine nucleotide binding protein: EC, endogenous compound
*guanosine triphosphatase: EC, endogenous compound
*histamine derivative: AN, drug analysis
*histamine derivative: CM, drug comparison
*histamine derivative: DV, drug development
***histamine h2 receptor: EC, endogenous compound**
2 octylhistamine: AN, drug analysis
2 octylhistamine: CM, drug comparison
2 octylhistamine: DV, drug development
3 (2 hydroxyethyl)imidazole derivative: DV, drug development
3 (2 hydroxyethyl)imidazole derivative: AN, drug analysis
3 (2 hydroxyethyl)imidazole derivative: CM, drug comparison
pertussis toxin
unclassified drug
RN (guanosine triphosphatase) 9059-32-9; (pertussis toxin) 70323-44-3

L93 ANSWER 4 OF 15 EMBASE
on STN
AN 96152859 EMBASE
DN 1996152859
TI A galanin-mastoparan chimeric peptide activates the Na+, K+-ATPase and reverses its inhibition by ouabain.
AU Langel U.; Pooga M.; Kairane C.; Zilmer M.; Bartfai T.
CS Dept. Neurochemistry/Neurotoxicology, Arrheniuslaboratories, Stockholm University,S-106 91 Stockholm, Sweden
SO Regulatory Peptides, (1996) 62/1 (47-52).
ISSN: 0167-0115 CODEN: REPPDY
CY Netherlands
DT Journal; Article
FS 002 Physiology
008 Neurology and Neurosurgery
029 Clinical Biochemistry
037 Drug Literature Index
LA English
SL English
AB The effect of the neuropeptide galanin, the wasp venom toxin **amphiphilic** peptide toxin mastoparan and the chimeric peptide, galparan, consisting of N-terminal 13 amino acids of neuropeptide galanin linked at C-terminus to mastoparan amide (and its inactive analog Mas17) on the activity of Na+,K+-ATPase has been studied. Mastoparan inhibits the activity of the Na+,K+-ATPase with IC50 = 7.5 .mu.M and also reduces the cooperativity for Na+ and K+, respectively, while galanin has no effect on the Na+,K+-ATPase activity. The chimeric peptide, galanin(1-13)-mastoparan amide (galparan), exhibits biphasic interaction with Na+,K+-ATPase, it activates the enzyme at maximal stimulating concentration of 4 .mu.M followed by inhibition of the enzyme with IC50, of 100 .mu.M. At maximum stimulating concentration (4 .mu.M), galparan partly reduces the cooperativity only for Na+ and it also counteracts the inhibitory effect of ouabain on Na+,K+-ATPase. Galparan's stimulatory effect was influenced by ATP. The chimeric peptide [19Lys,26Leu]-galparan, containing the inactive analog of mastoparan (Mas17), has no effects on rat brain Na+,K+-ATPase activity. Both chimeric peptides galparan and [19Lys,26Leu]-galparan are high-affinity galanin receptor ligands with IC50 of 6.4 nM and 0.71 nM, respectively, while galanin (1-13) and mastoparan alone have significantly lower affinity for the galanin receptor, IC50 Of 125 nM and 1 .mu.M, respectively. The ability of chimeric peptides to bind to galanin receptors does not correlate with their effects on the Na+,K+-ATPase.
CT Medical Descriptors:
*enzyme activity
*frontal cortex
animal tissue
article
binding site
drug receptor binding
membrane binding
nonhuman
priority journal
rat
Drug Descriptors:
*galanin: PD, pharmacology
*galanin derivative: PD, pharmacology
*mastoparan: PD, pharmacology
*ouabain
adenosine triphosphatase (potassium sodium): EC, endogenous compound

adenosine triphosphate
chimeric protein
galanin receptor: EC, endogenous compound
galparan: PD, pharmacology
neuropeptide
wasp venom
unclassified drug
RN (galanin) 88813-36-9; (mastoparan) 72093-21-1; (ouabain) 11018-89-6, 630-60-4; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5

L93 ANSWER 5 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 96074849 EMBASE
DN 1996074849
TI G-Protein-coupled receptors in HL-60 human leukemia cells.
AU Klinker J.F.; Wenzel-Seifert K.; Seifert R.
CS Howard Hughes Medical Institute, Stanford University, Medical Center,Stanford, CA 94305, United States
SO General Pharmacology, (1996) 27/1 (33-54).
ISSN: 0306-3623 CODEN: GEPHDP
CY United States
DT Journal; General Review
FS 016 Cancer
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB 1. HL-60 human leukemia cells are a widely employed model system for the analysis of signal transduction processes mediated via regulatory heterotrimeric guanine nucleotide-binding proteins (G-proteins). HL-60 promyelocytes are pluripotent and can be differentiated into neutrophilic or monocytic cells. 2. HL-60 cells express formyl peptide-, complement C5a-, leukotriene B4 (LTB4)- and platelet-activating factor receptors, receptors for purine and pyrimidine nucleotides, histamine H1- and H2-receptors .beta.2-adrenoceptors and prostaglandin receptors. 3. The major G-proteins in HL-60 cells are pertussis toxin (PTX) sensitive G(i)-proteins (G(i2) > G(i3)). G(s)-proteins and G-proteins of the G(q)-family (e.g., G16) are expressed, too. 4. G-protein-regulated effector systems in HL-60 cells are adenylyl cyclase and phospholipase C-.beta.2 (PLC-.beta.2) and, possibly, phospholipase D (PLD), nonselective cation (NSC) channels and NADPH oxidase. 5. The expression of signal transduction pathways in HL-60 cells strongly depends on the differentiation state of cells. 6. Formyl peptides, via G(i) proteins, mediate activation of PLC, PLD, NSC channels, NADPH oxidase and azurophilic granule release and are referred to as full secretagogues. In dibutyryl cAMP (Bt2cAMP)-differentiated HL-60 cells, C5a and LTB4 are partial and incomplete secretagogues, respectively. There are substantial differences in the G(i)-protein activations induced by formyl peptides, C5a and LTB4. 7. In HL-60 promyelocytes, purine and pyrimidine nucleotides mediate activation of PLC and NSC channels largely via PTX-insensitive G-proteins and induce functional differentiation. In Bt2cAMP-differentiated HL-60 cells, they additionally activate PLD, NADPH oxidase and granule release via PTX-sensitive and -insensitive pathways. ATP and UTP are partial secretagogues. Multiple types of receptors (i.e., P(2Y)- and P(2U)-receptors and pyrimidinocyeptors) may mediate the effects of nucleotides in HL-60 cells. 8. Bt2cAMP and 1.alpha.,25-dihydroxycholecalciferol-differentiated HL-60 cells express H1- receptors coupled to G(i)-proteins and PTX-insensitive G-proteins. In the former cells, histamine mediates activation of PLC and NSC channels, and in the latter, activation of NSC channels. Histamine is an incomplete secretagogue in these cells. 9. HL-60 promyelocytes express H2-receptors coupled to adenylyl cyclase, PLC, and NSC channels. There are substantial differences in the agonist/antagonist profiles of H2-receptors receptor mediated cAMP formation and rises in cytosolic Ca2+ concentration, indicative of the involvement of different H2-receptors receptor subtypes. H2-receptors mediate functional differentiation of HL-60 cells. 10. Certain cationic-amphiphilic histamine receptor ligands (i.e., 2 substituted histamines, lipophilic guanidines, and a histamine trifluoromethyl toluidide derivative) show stimulatory effects in HL-60 cells that are attributable to receptor independent activation of G(i)-proteins.
CT Medical Descriptors:
*leukemia cell
*signal transduction

cation channel
cell differentiation
cell strain hl 60
human
human cell
model
monocyte
neutrophil
priority journal
promyelocyte
review
Drug Descriptors:
*adenylate cyclase: EC, endogenous compound
*guanine nucleotide binding protein: EC, endogenous compound
*phospholipase c: EC, endogenous compound
***receptor: EC, endogenous compound**
adenosine triphosphate: PD, pharmacology
beta 2 adrenergic receptor: EC, endogenous compound
bucladesine: PD, pharmacology
calcitriol: PD, pharmacology
complement component c5a: PD, pharmacology
complement component c5a receptor: EC, endogenous compound
formylpeptide: PD, pharmacology
formylpeptide receptor: EC, endogenous compound
histamine: PD, pharmacology
histamine derivative: PD, pharmacology
histamine h1 receptor: EC, endogenous compound
histamine h2 receptor: EC, endogenous compound
inhibitory guanine nucleotide binding protein: EC, endogenous compound
leukotriene b4: PD, pharmacology
leukotriene b4 receptor: EC, endogenous compound
pertussis toxin: TO, drug toxicity
phospholipase d: EC, endogenous compound
prostaglandin receptor: EC, endogenous compound
purine nucleotide: PD, pharmacology
purine receptor: EC, endogenous compound
pyrimidine nucleotide: PD, pharmacology
reduced nicotinamide adenine dinucleotide phosphate oxidase: EC, endogenous compound
stimulatory guanine nucleotide binding protein: EC, endogenous compound
thrombocyte activating factor receptor: EC, endogenous compound
unindexed drug
uridine triphosphate: PD, pharmacology
unclassified drug
RN (adenylate cyclase) 9012-42-4; (phospholipase c) 9001-86-9; (adenosine triphosphate) 15237-44-2, 56-65-5, 987-65-5; (bucladesine) 16980-89-5, 362-74-3; (calcitriol) 32222-06-3, 32511-63-0, 66772-14-3; (histamine) 51-45-6, 56-92-8, 93443-21-1; (leukotriene b4) 71160-24-2; (pertussis toxin) 70323-44-3; (phospholipase d) 9001-87-0; (reduced nicotinamide adenine dinucleotide phosphate oxidase) 9032-22-8; (uridine triphosphate) 63-39-8

L93 ANSWER 6 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 95364319 EMBASE
DN 1995364319
TI Targeted transfection of human hepatoma cells with a combination of lipospermine and neo-galactolipids.
AU Kichler A.; Remy J.-S.; Behr J.-P.; Schuber F.
CS Laboratoire de Chimie Bioorganique, Faculte de Pharmacie, CNRS URA 1386, 74 Route du Rhin,67401 Strasbourg-Illkirch Cedex, France
SO Journal of Liposome Research, (1995) 5/4 (735-745).
ISSN: 0898-2104 CODEN: JLREE7
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Optimal in vitro gene delivery with (poly)cationic **amphiphiles** requires an excess of cationic charges with respect to DNA phosphates. We have developed targeted transfection systems based on electrically neutral lipospermine/DNA particles, to which synthetic tri-antennary galactose ligands were conjugated to provide an interaction with cells, such as HepG2 cells, that express Gal/GalNAc receptors at their surface.

Transfection, which was cell specific, increases .simeq. 1000-fold with 25% neogalactolipid, i.e. approaching the value observed with optimized positively charged transfection complexes. Unexpectedly, neutral particles containing thiol-reactive phospholipids, were also efficient gene delivery systems, although non cell specific.

CT Medical Descriptors:
*gene targeting
*hepatoma cell: DT, drug therapy
*genetic transfection
article
binding affinity
binding site
gene induction
gene therapy
opsonization
plasmid
priority journal
Drug Descriptors:
cell surface receptor
*amphophile: PR, pharmaceutics
*liposome: CB, drug combination
*liposome: DV, drug development
*spermine: CB, drug combination
*spermine: DV, drug development
*spermine: DT, drug therapy
*spermine: PR, pharmaceutics
lipospermine
transfectam
unclassified drug

RN (spermine) 306-67-2, 71-44-3
CN (1) Transfectam
CO (1) Promega

L93 ANSWER 7 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 95321821 EMBASE
DN 1995321821
TI The **amphiphilic** peptide adenoregulin enhances agonist binding to A1- adenosine receptors and [35S]GTP.gamma.S to brain membranes.
AU Moni R.W.; Romero F.S.; Daly J.W.
CS National Institutes of Health, Bldg. 8,Bethesda, MD 20892, United States
SO Cellular and Molecular Neurobiology, (1995) 15/4 (465-493).
ISSN: 0272-4340 CODEN: CMNEDI
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
029 Clinical Biochemistry
LA English
SL English
AB 1. Adenoregulin is an amphilic peptide isolated from skin mucus of the tree frog, Phyllomedusa bicolor. Synthetic adenoregulin enhanced the binding of agonists to several G-protein-coupled receptors in rat brain membranes. 2. The maximal enhancement of agonist binding, and in parentheses, the concentration of adenoregulin affording maximal enhancement were as follows: 60% (20 .mu.M) for A1-adenosine receptors, 30% (100 .mu.M) for A(2a)-adenosine receptors, 20% (2 .mu.M) for .alpha.2-adrenergic receptors, and 30% (10 .mu.M) for 5HT(1A) receptors. High affinity agonist binding for A1-, .alpha.2-, and 5HT(1A)-receptors was virtually abolished by GTP.gamma.S in the presence of adenoregulin, but was only partially abolished in its absence. Magnesium ions increased the binding of agonists to receptors and reduced the enhancement elicited by adenoregulin. 3. The effect of adenoregulin on binding of N6-cyclohexyladenosine ([3H]CHA) to A1-receptors was relatively slow and was irreversible. Adenoregulin increased the B(max) value for [3H]CHA binding sites, and the proportion of high affinity states, and slowed the rate of [3H]CHA dissociation. Binding of the A1-selective antagonist, [3H]DPCPX, was maximally enhanced by only 13% at 2 .mu.M adenoregulin. Basal and A1-adenosine receptor-stimulated binding of [35S]GTP.gamma.S were maximally enhanced 45% and 23%, respectively, by 50 .mu.M adenoregulin. In CHAPS-solubilized membranes from rat cortex, the binding of both [3H]CHA and [3H]DPCPX were enhanced by adenoregulin. Binding of [3H]CHA to membranes from DDT1 MF-2 cells was maximally enhanced 17% at 20 .mu.M adenoregulin. In intact DDT1 MF-2 cells, 20 .mu.M adenoregulin did not potentiate the inhibition of cyclic AMP accumulation mediated via the adenosine A1 receptor. 4. It is proposed that adenoregulin enhances agonist binding through a mechanism involving enhancement of guanyl nucleotide exchange at

G- proteins, resulting in a conversion of receptors into a high affinity state complexed with guanyl nucleotide-free G-protein.

CT Medical Descriptors:
*brain membrane
*receptor binding
animal tissue
article
binding kinetics
brain cortex
cerebellum
controlled study
corpus striatum
frog
hippocampus
nonhuman
priority journal
rat
receptor affinity
Drug Descriptors:
***adenosine a1 receptor**
alpha 2 adrenergic receptor
serotonin 1a receptor
*amphophile
*guanine nucleotide binding protein: EC, endogenous compound
*guanosine 5' o (3 thiotriphosphate)
*peptide
8 cyclopentyl 1,3 dipropylxanthine
adenoregulin
cyclic amp: EC, endogenous compound
cyclohexyladenosine
magnesium ion
sodium chloride
unclassified drug

RN (guanosine 5' o (3 thiotriphosphate)) 37589-80-3; (8 cyclopentyl 1,3 dipropylxanthine) 102146-07-6; (cyclic amp) 60-92-4; (cyclohexyladenosine) 36396-99-3; (magnesium ion) 22537-22-0; (sodium chloride) 7647-14-5

L93 ANSWER 8 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 95176244 EMBASE
DN 1995176244
TI The cholesterol derivative of a triantennary galactoside with high affinity for the hepatic asialoglycoprotein receptor: A potent cholesterol lowering agent.
AU Biessen E.A.L.; Broxterman H.; Van Boom J.H.; Van Berkel T.J.C.
CS Division of Biopharmaceutics, Leiden-Amsterdam Drug Research Ctr., P.O. Box 9503,2300 RA Leiden, Netherlands
SO Journal of Medicinal Chemistry, (1995) 38/11 (1846-1852). ISSN: 0022-2623 CODEN: JMCMAR
CY United States
DT Journal; Article
FS 018 Cardiovascular Diseases and Cardiovascular Surgery
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Cholesterol-derivatized galactosides have been devised in order to induce liver uptake of lipoproteins via the galactose-recognizing asialoglycoprotein receptor in the liver. In this study we describe the derivatization of a newly developed triantennary cluster galactoside having high affinity for the asialoglycoprotein receptor, N-[[tris-O-(3,6,9-trioxaundecanyl-.beta.-D- galactopyranosyl)methoxymethyl]methyl]-N(n)-[1-(6-methyladipyl)]glycinamid e (TG(20.ANG.)) with cholesterol. Hereto, TG(20.ANG.) was coupled to glycine-(5-cholesten-3.beta.-yl ester) in the presence of (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate, affording N-[[tris-O-(3,6,9-trioxaundecanyl-.beta.-D-galactopyranasyl)methoxymethyl]me t hyl]- N(.alpha.)[1-(6-(5-cholesten-3.beta.-yloxy)glycyl)adipyl]glycinami de (TG(20.ANG.)C) in 46% yield. This compound is an **amphiphilic**, water-soluble compound. In aqueous solution it readily formed small micelles (4.9 .+-. 1.2 nm) consisting of approximately 20 molecules. Upon incubation with human serum, TG(20.ANG.)C spontaneously incorporated into the most prominent serum lipoproteins, i.e., low-density lipoprotein (LDL) and high-density lipoprotein (HDL), thereby inducing an increase in buoyant density of these lipoproteins. The integrity of HDL and LDL, as judged from particle size analysis of both lipoproteins, was not altered

by incubation with up to 0.33% of TG(20.ANG.)C (w/v). Following intravenous bolus injection into rats, TG(20.ANG.)C induced a dose-dependent decrease in the serum cholesterol content of maximally 44%, at a dose of 1.9 mg kg-1. This makes TG(20.ANG.)C at least 30-fold more effective than the previously developed .cntdot. N-[[tris-O-(.beta.-D-galactopyranosyl)methyl]methyl]- N(.alpha.)[4-(5-cholesten-3.beta.-yloxy)succinyl]glycinamide (TG(4.ANG.)C), provided with a cluster galactoside that displayed a 2000-fold lower affinity for the asialoglycoprotein receptor than TG(20.ANG.). In conclusion, the hypocholesterolemic activity of a cholesterylated galactoside can be strongly enhanced by using a cluster galactoside with higher affinity for the asialoglycoprotein receptor.

CT Medical Descriptors:
*drug receptor binding
*hypercholesterolemia
animal experiment
article
cholesterol liver level
cholesterol transport
dose response
drug potency
drug synthesis
human
male
nonhuman
rat
receptor affinity
Drug Descriptors:
***asialoglycoprotein receptor**
*hypocholesterolemic agent: DV, drug development
*hypocholesterolemic agent: DO, drug dose
*hypocholesterolemic agent: PD, pharmacology
*hypocholesterolemic agent: CM, drug comparison
(benzotriazol 1 yloxy)tris(dimethylamino)phosphonium hexafluorophosphate: DV, drug development
glycine 5 cholesten 3beta yl ester: DV, drug development
n [[[tris o (beta d galactopyranosyl) 3,6,9 trioxaundecanoxy]methoxy]methyl] n alpha [1 (6 methyladipyl)]glycinamide: DV, drug development
n [[[tris o (beta d galactopyranosyl) 3,6,9 trioxaundecanoxy]methoxy]methyl] n alpha [1 (6 methyladipyl)]glycinamide: DO, drug dose
n [[[tris o (beta d galactopyranosyl) 3,6,9 trioxaundecanoxy]methoxy]methyl] n alpha [1 (6 methyladipyl)]glycinamide: PD, pharmacology
n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]methyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: DV, drug development
n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]methyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: PD, pharmacology
n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]methyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: DO, drug dose
n [tris o (3,6,9 trioxaundecanyl beta d galactopyranosyl)methoxymethyl]methyl n alpha [1 [6 (5 cholesten 3beta yloxy)glycyl]adipyl]glycinamide: CM, drug comparison
n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten 3beta yl)succinyl]glycinamide: CM, drug comparison
n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten 3beta yl)succinyl]glycinamide: DV, drug development
n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten 3beta yl)succinyl]glycinamide: DO, drug dose
n [tris o (beta d glucopyranosyl)methyl]methyl n alpha [4 o (5 cholesten 3beta yl)succinyl]glycinamide: PD, pharmacology
unclassified drug

CO Bissendorf (Germany)

L93 ANSWER 9 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 95091592 EMBASE
DN 1995091592
TI Cationic-**amphiphilic** arpromidine-derived guanidines and a histamine trifluoromethyl-toluidide derivative may activate pertussis toxin-sensitive G-proteins by a receptor-independent mechanism.
AU Hageluken A.; Burde R.; Nurnberg B.; Harhammer R.; Buschauer A.; Seifert R.
CS Institut fur Pharmazie, Universitat Regensburg,D-93040 Regensburg, Germany
SO Naunyn-Schmiedeberg's Archives of Pharmacology, (1995) 351/3 (305-308).

ISSN: 0028-1298 CODEN: NSAPCC
CY Germany
DT Journal; Article
FS 016 Cancer
025 Hematology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Formyl peptides activate superoxide anion (O2-) formation in human neutrophils and in HL-60 cells via pertussis toxin (PTX)-sensitive guanine nucleotide-binding proteins (G-proteins), and histamine (HA) mediates inhibition of O2- formation via H2-receptors. We have studied the effects of lipophilic arpromidine-derived guanidines, which are potent, full H2-receptor agonists in the guinea pig atrium, on O2- formation and on activation of O-proteins in HL-60 membranes and on purified G-proteins. We have also studied the effects of a HA trifluoromethyl-toluidide derivative (HTMT), a cationic-**amphiphilic** HA derivative which activates O2- formation in HL-60 cells through a mechanism which is independent of known HA receptor subtypes, on G-protein activation. Guanidines, at concentrations, up to 30 .mu.mol/l inhibited and, at concentrations above 30 .mu.mol/l, enhanced formyl peptide-induce O2- formation in neutrophils. In HL-60 cells, guanidines per se activated O2- formation. The stimulatory effects of guanidines on O2- formation were not inhibited by H1- or H2-receptor antagonists. In HL-60 membranes, guanidines and HTMT, activated high-affinity GTPase in a PTX-sensitive manner. These substances also increased GTP hydrolysis effected by transducin and G(i)/G(o)-proteins. Our data suggest that lipophilic guanidines and HTMT may act as receptor-independent activators of PTX-sensitive G-proteins, resulting in stimulation of O2- formation.
CT Medical Descriptors:
*leukemia cell
*neutrophil
article
cell strain hl 60
concentration response
controlled study
drug mechanism
drug synthesis
human
human cell
hydrolysis
lipophilicity
Drug Descriptors:
***histamine h2 receptor**
*arpromidine: PD, pharmacology
*guanidine derivative: DV, drug development
*guanidine derivative: PD, pharmacology
*guanine nucleotide binding protein: EC, endogenous compound
*guanosine triphosphate
*histamine agonist: PD, pharmacology
1 [3 (3,4 dichlorophenyl) 3 (2 pyridyl)propyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: DV, drug development
1 [3 (3,4 dichlorophenyl) 3 (2 pyridyl)propyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: PD, pharmacology
1 [3 (3,4 dichlorophenyl) 3 phenylpropyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: DV, drug development
1 [3 (3,4 dichlorophenyl) 3 phenylpropyl] 3 [3 (1h imidazol 4 yl)propyl]guanidine: PD, pharmacology
6 [2 (4 imidazolyl)ethylamino] n (4 trifluoromethylphenyl)heptanamide: DV, drug development
6 [2 (4 imidazolyl)ethylamino] n (4 trifluoromethylphenyl)heptanamide: PD, pharmacology
amphophile: PD, pharmacology
bu e 64
bu e 82
cation: PD, pharmacology
cimetidine: PD, pharmacology
diphenhydramine: PD, pharmacology
formylmethionylleucylphenylalanine: PD, pharmacology
guanosine triphosphatase: EC, endogenous compound
histamine derivative: DV, drug development
histamine derivative: PD, pharmacology
histamine h1 receptor antagonist: PD, pharmacology
histamine h2 receptor agonist: PD, pharmacology

histamine h2 receptor antagonist: PD, pharmacology
inhibitory guanine nucleotide binding protein
pertussis toxin: TO, drug toxicity
superoxide: EC, endogenous compound
transducin
unclassified drug

RN (arpromidine) 106669-71-0; (guanosine triphosphate) 86-01-1; (cimetidine) 51481-61-9, 70059-30-2; (diphenhydramine) 147-24-0, 58-73-1; (guanosine triphosphatase) 9059-32-9; (pertussis toxin) 70323-44-3; (superoxide) 11062-77-4; (transducin) 94699-82-8
CN Bu e 64; Bu e 82
CO Cookson (United Kingdom)

L93 ANSWER 10 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 95081931 EMBASE
DN 1995081931
TI Structural and conformational requirements for human calcitonin activity: Design, synthesis, and study of lactam-bridged analogues.
AU Kapurniotu A.; Taylor J.W.
CS Department of Chemistry, Rutgers University, P.O. Box 939,Piscataway, NJ 08855-0939, United States
SO Journal of Medicinal Chemistry, (1995) 38/5 (836-847).
ISSN: 0022-2623 CODEN: JMCMAR
CY United States
DT Journal; Article
FS 003 Endocrinology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The conformational and pharmacological effects of the introduction of conformational constraints in the form of i-(i + 4) lactam-bridges in the potential **amphiphilic** .alpha.-helical region (8-21) of human calcitonin (hCT) were studied. The following three cyclic hCT analogues were synthesized: cyclo17,21-[Lys17,Asp21]hCT (1), cyclo17,21-[Asp17,Lys21]hCT (2) and cyclo10,14-[Lys10,Asp14]hCT (3). For their syntheses, solid-phase methodology was used in combination with either direct side chain to side chain cyclization on the solid support or a segment-condensation strategy. Circular dichroism studies in aqueous buffer, pH 7.0, indicated that the conformational effects were different for each lactam bridge introduced. Significant induction of .alpha.-helical structure was observed only for peptide 3. In contrast, peptide 1 and hCT had similar CD spectra, indicative of mixed disordered and .beta.-sheet conformations, and peptide 2 had a weaker spectrum consistent with the formation of a more ordered but nonhelical structure. In rat brain receptor binding assays, peptide 2 showed a nearly 80-fold higher potency than hCT or peptides 1 and 3. All three analogues stimulated adenylyl cyclase in the rat kidney membrane at 5-fold lower concentrations than hCT and with similar maximal effects. In vivo hypocalcemic assays, performed in mice by analysis of serum calcium levels 1 h after sc injection, indicated that peptide 2 had similar maximal effects to hCT and was 10-20 times more potent than hCT at doses giving half- maximal effects. In contrast, peptides 1 and 3 were not significantly more potent than hCT. Our findings indicate compatibility of all three lactam bridges and, most probably, also the **amphiphilic** .alpha.-helix, with the pharmacological activities of hCT. However, the properties of peptide 2 also suggest that another conformation, possibly a type I .beta.-turn involving residues 17-20, may play an important role. A multistep mechanism of receptor recognition by hCT that might account for these results is discussed.
CT Medical Descriptors:
*cyclization
*hypocalcemia
amino acid substitution
animal experiment
animal tissue
article
basolateral membrane
brain membrane
calcium blood level
circular dichroism
controlled study
drug conformation
drug design
drug effect

drug potency
drug receptor binding
drug synthesis
female
male
mouse
nonhuman
rat
structure activity relation
subcutaneous drug administration
Drug Descriptors:
***calcitonin receptor**
brain receptor
*calcitonin: AN, drug analysis
*calcitonin: DV, drug development
*calcitonin: PD, pharmacology
*calcitonin derivative: DV, drug development
*calcitonin derivative: PD, pharmacology
*calcitonin derivative: AN, drug analysis
*lactam
adenylate cyclase: EC, endogenous compound
aspartic acid
calcitonin[10 lysine,14 aspartic acid lactam]: PD, pharmacology
calcitonin[10 lysine,14 aspartic acid lactam]: DV, drug development
calcitonin[10 lysine,14 aspartic acid lactam]: AN, drug analysis
calcitonin[17 aspartic acid,21 lysine lactam]: AN, drug analysis
calcitonin[17 aspartic acid,21 lysine lactam]: PD, pharmacology
calcitonin[17 aspartic acid,21 lysine lactam]: DV, drug development
calcitonin[17 lysine,21 aspartic acid lactam]: AN, drug analysis
calcitonin[17 lysine,21 aspartic acid lactam]: PD, pharmacology
calcitonin[17 lysine,21 aspartic acid lactam]: DV, drug development
calcium ion: EC, endogenous compound
lysine
salcatonin
unclassified drug
RN (calcitonin) 12321-44-7, 21215-62-3, 9007-12-9; (adenylate cyclase) 9012-42-4; (aspartic acid) 56-84-8, 6899-03-2; (calcium ion) 14127-61-8; (lysine) 56-87-1, 6899-06-5, 70-54-2; (salcatonin) 47931-85-1
CO Bachem (United States); Aldrich; Fisher; Fluka; Sigma; Amersham

L93 ANSWER 11 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 94366690 EMBASE
DN 1994366690
TI Cholesterol homeostasis. Modulation by **amphiphiles**.
AU Lange Y.; Steck T.L.
CS Dept. of Pathology, Rush-Presbyterian-SLMC, 1653 W. Congress Pkwy.,Chicago, IL 60612, United States
SO Journal of Biological Chemistry, (1994) 269/47 (29371-29374).
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Diverse **amphiphiles** act on cellular cholesterol metabolism as if signaling regulatory sites. One class (oxysterols) mimics the homeostatic effects of excess cell cholesterol, inhibiting cholesterol biosynthesis and stimulating plasma membrane cholesterol esterification. A second class of **amphiphiles** has effects precisely opposite to the oxysterols, i.e. they immediately inhibit plasma membrane cholesterol esterification and progressively induce 3- hydroxy-3-methylglutaryl-coenzyme A reductase activity and cholesterol biosynthesis. This second class of agents includes steroids, hydrophobic amines, phenothiazines, ionophores, colchicine, cytochalasins, and lysophosphatides, most of which interact with P-glycoproteins. These data support a general hypothesis describing cellular cholesterol homeostasis. (a) Proteins regulating sterol metabolism are embedded in intracellular membranes where their activities are governed by the local level of cholesterol. (b) Excess plasma membrane and lysosomal cholesterol circulates through those intracellular membranes and sets the homeostatic activities therein. (c) The two classes of agents mentioned above affect cholesterol homeostasis by increasing or decreasing, respectively, the ambient level of cholesterol at the sites of regulation.

CT Medical Descriptors:
*cholesterol esterification
*cholesterol synthesis
animal cell
article
cholesterol metabolism
controlled study
drug antagonism
enzyme activity
fibroblast
hepatoma cell
human
human cell
nonhuman
priority journal
rat
Drug Descriptors:
***low density lipoprotein receptor**
*amphophile: IT, drug interaction
*amphophile: PD, pharmacology
*amphophile: CB, drug combination
*cholesterol
*glycoprotein p: EC, endogenous compound
*hydroxymethylglutaryl coenzyme a reductase: EC, endogenous compound
*hydroxysterol: IT, drug interaction
*hydroxysterol: PD, pharmacology
*sterol derivative: PD, pharmacology
*sterol derivative: IT, drug interaction
*sterol derivative: CB, drug combination
25 hydroxycholesterol: CB, drug combination
25 hydroxycholesterol: PD, pharmacology
25 hydroxycholesterol: IT, drug interaction
3beta (2 diethylaminoethoxy)androst 5 en 17 one: PD, pharmacology
3beta (2 diethylaminoethoxy)androst 5 en 17 one: IT, drug interaction
3beta (2 diethylaminoethoxy)androst 5 en 17 one: CB, drug combination
chloroquine: IT, drug interaction
chloroquine: CB, drug combination
chloroquine: PD, pharmacology
colchicine: PD, pharmacology
cytochalasin a: CB, drug combination
cytochalasin a: PD, pharmacology
cytochalasin a: IT, drug interaction
cytochalasin b: CB, drug combination
cytochalasin b: IT, drug interaction
cytochalasin b: PD, pharmacology
cytochalasin d: CB, drug combination
cytochalasin d: PD, pharmacology
cytochalasin d: IT, drug interaction
estradiol: PD, pharmacology
fluoride sodium
hydroxysterol derivative: CB, drug combination
imipramine: PD, pharmacology
low density lipoprotein: EC, endogenous compound
lysophosphatidylcholine: PD, pharmacology
monensin: PD, pharmacology
monensin: IT, drug interaction
monensin: CB, drug combination
nigericin: PD, pharmacology
nigericin: IT, drug interaction
nigericin: CB, drug combination
oleic acid
oxysterol derivative: IT, drug interaction
oxysterol derivative: CB, drug combination
oxysterol derivative: PD, pharmacology
pregnenolone: PD, pharmacology
progesterone: IT, drug interaction
progesterone: PD, pharmacology
progesterone: CB, drug combination
testosterone: PD, pharmacology
trifluoperazine: PD, pharmacology
unclassified drug

RN (cholesterol) 57-88-5; (hydroxymethylglutaryl coenzyme a reductase) 37250-24-1; (25 hydroxycholesterol) 2140-46-7; (3beta (2 diethylaminoethoxy)androst 5 en 17 one) 3039-71-2; (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7; (colchicine) 64-86-8; (cytochalasin a) 14110-64-6; (cytochalasin b) 14930-96-2; (cytochalasin d) 22144-77-0;

(estradiol) 50-28-2; (fluoride sodium) 51668-54-3, 7681-49-4, 79933-27-0; (imipramine) 113-52-0, 50-49-7; (lysophosphatidylcholine) 93794-93-5; (monensin) 17090-79-8, 22373-78-0; (nigericin) 28380-24-7; (oleic acid) 112-80-1, 115-06-0; (pregnenolone) 145-13-1; (progesterone) 57-83-0; (testosterone) 58-22-0; (trifluoperazine) 117-89-5, 440-17-5
CN U 18666 a

L93 ANSWER 12 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 94146405 EMBASE
DN 1994146405
TI The H1 receptor agonist 2-(3-chlorophenyl)histamine activates G(i) proteins in HL-60 cells through a mechanism that is independent of known histamine receptor subtypes.
AU Seifert R.; Hageluken A.; Hoer A.; Hoer D.; Grunbaum L.; Offermanns S.; Schwaner I.; Zingel V.; Schunack W.; Schultz G.
CS Institut fur Pharmakologia, Freie Universitat Berlin, Thielallee 69-73,D-14195 Berlin, Germany
SO Molecular Pharmacology, (1994) 45/4 (578-586).
ISSN: 0026-895X CODEN: MOPMA3
CY United States
DT Journal; Article
FS 030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB In dibutyryl-cAMP-differentiated HL-60 cells, histamine H1 and formyl peptide receptors mediate increases in the cytosolic Ca2+ concentration ([Ca2+](i)) via pertussis toxin-sensitive G proteins of the G(i) family. We compared the effects of 2-(3-chlorophenyl)-histamine (CPH) [2-[2-(3-chlorophenyl)-1H-imidazol-4-yl] ethanamine], one of the most potent and selective H1 receptor agonists presently available, with those of histamine and N-formyl-L-methionyl-L-leucyl-L-phenylalanine (fMLP) in these cells. CPH increased [Ca2+](i) through Ca2+ mobilization and Ca2+ influx. Unlike histamine-induced rises in [Ca2+](i), those induced by CPH were not desensitized in a homologous manner, and there was no cross-desensitization between CPH and histamine. Like fMLP, CPH activated phospholipases C and D, tyrosine phosphorylation, superoxide anion formation, and azurophilic granule release. The effects of CPH on [Ca2+](i), phospholipase D, and superoxide anion formation were inhibited by pertussis toxin. CPH and fMLP stimulated high affinity GTP hydrolysis by G(i) proteins in HL-60 membranes. They also enhanced binding of guanosine-5'-O-(3-thio)triphosphate and GTP azidoanilide to, and cholera toxin-catalyzed ADP-ribosylation of G(i) protein .alpha. subunits. Histamine receptor antagonists did not inhibit the stimulatory effects of CPH, and CPH did not reduce fMLP binding in HL-60 membranes. Our data suggest that CPH activates G(i) proteins in HL-60 cells through a receptor agonist- like mechanism that is, however, independent of known histamine receptor subtypes and formyl peptide receptors. CPH may be an agonist at an as yet unknown histamine receptor subtype or by analogy with other cationic- **amphiphilic** substances, may activate G proteins directly. Future studies will have to take into consideration the fact that CPH, in addition to activating H1 receptors, may show other, most unexpected, stimulatory effects on G protein mediated signal transduction processes.
CT Medical Descriptors:
article
calcium cell level
calcium mobilization
calcium transport
cell strain hl 60
controlled study
drug activity
drug mechanism
enzyme activation
human
human cell
Drug Descriptors:
***histamine h1 receptor**
receptor subtype
*histamine h1 receptor agonist: CM, drug comparison
*histamine h1 receptor agonist: PD, pharmacology
2 (3 chlorophenyl)histamine: CM, drug comparison
2 (3 chlorophenyl)histamine: PD, pharmacology
calcium ion: EC, endogenous compound
formylmethionylleucylphenylalanine: CM, drug comparison

guanosine 5' o (3 thiotriphosphate)
histamine: CM, drug comparison
inhibitory guanine nucleotide binding protein
pertussis toxin
phospholipase c
phospholipase d
unclassified drug
RN (calcium ion) 14127-61-8; (guanosine 5' o (3 thiotriphosphate)) 37589-80-3; (histamine) 51-45-6, 56-92-8, 93443-21-1; (pertussis toxin) 70323-44-3; (phospholipase c) 9001-86-9; (phospholipase d) 9001-87-0

L93 ANSWER 13 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 93039519 EMBASE
DN 1993039519
TI Differential insertion of insulin receptor complexes into Triton X-114 bilayer membranes. Evidence for a differential accessibility of the membrane-exposed receptor domain.
AU Florke R.-R.; Klein H.W.; Reinauer H.
CS Diabetes-Forschungsinstitut, Auf'm Hennekamp 65,W-4000 Dusseldorf, Germany
SO European Journal of Biochemistry, (1993) 211/1-2 (241-247).
ISSN: 0014-2956 CODEN: EJBCAI
CY Germany
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB In the present study, the Triton X-114 phase-separation system has been used to characterize molecular properties of the membrane-exposed domain of an integral-membrane hormone receptor. This approach provides novel details of the structure/function relationship of insulin receptors. Upon raising the temperature of a micellar Triton X-114 solution above the cloud-point, a detergent enriched phase pellets and coprecipitates 95% of the purified insulin-free (.alpha..beta.)2 receptors. In contrast, 83% of the hormone bound (.alpha..beta.)2 receptor complexes prefer the detergent-depleted phase, exhibiting prominent properties of non-membraneous proteins. Kinetic studies show that, following insulin binding, the **amphiphilicity** of the receptor complexes is immediately altered. Only monodisperse (.alpha..beta.)2 complexes were detected when receptor/insulin complexes of the detergent-depleted phase were analyzed by detergent-free sucrose density centrifugation in the presence of 10 nM insulin. These results can be explained in the light of the lipid-bilayer-like organization of the precipitating Triton X-114; hormone-induced intramolecular alterations of (.alpha..beta.)2 receptors appear to fundamentally restrict access to the membrane-exposed receptor domain. Basically, different molecular properties are found for .alpha..beta. receptors. Only 67% of the insulin-free .alpha..beta. receptors coprecipitate with the Triton-X-114-enriched phase; following insulin binding the coprecipitation is only decreased to 42%. In contrast to (.alpha..beta.)2 receptors, formation of noncovalently aggregated receptor complexes, which are detected by sucrose density centrifugation, could account for the exclusion of .alpha..beta. receptor species from Triton X-114 membranes.
CT Medical Descriptors:
*receptor binding
*structure activity relation
article
human
human tissue
priority journal
Drug Descriptors:
***insulin receptor**
*insulin
triton x 114
unclassified drug
RN (insulin) 9004-10-8; (triton x 114) 9036-19-5

L93 ANSWER 14 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN 87182320 EMBASE
DN 1987182320
TI Synthesis of two glucagon antagonists: Receptor binding, adenylate cyclase, and effects on blood plasma glucose levels.
AU Gysin B.; Johnson D.G.; Trivedi D.; Hruby V.J.
CS Department of Chemistry, University of Arizona, Tucson, AZ 85721, United States

SO Journal of Medicinal Chemistry, (1987) 30/8.(1409-1415).
CODEN: JMCMAR
CY United States
DT Journal
FS 037 Drug Literature Index
029 Clinical Biochemistry
030 Pharmacology
LA English
AB In diabetes mellitus, hyperglycemia is often associated with elevated levels of glucagon in the blood. This suggests that glucagon (1) is a contributing factor in the metabolic abnormalities of diabetes mellitus. A glucagon-receptor antagonist would provide direct evidence for glucagon's role in diabetes mellitus. On the basis of careful consideration of conformational, **amphiphilic**, and structural factors, we have synthesized two new glucagon analogues with antagonist biological activities by using solid-phase methodology. These two new analogues, [Asp3,D-Phe4,Ser5,Lys17,18,Glu21]glucagon (2) and [D-Phe4,Tyr5,3,5-I2-Tyr10,Arg12,Lys17,18,Glu21]gluca gon (3), had IC50 values 5.4% and 50% those of glucagon, respectively, and showed no measurable adenylate cyclase activity. When tested in normal rats, 2 lowered plasma glucose levels and suppressed glucagon-mediated hyperglycemia 105 .+-. 8%, back to basal levels. Analgoue 3, which lowered the basal adenylate cyclase activity in rat liver plasma membranes, increased plasma glucose levels at very high concentration in vivo and inhibited glucagon-mediated hyperglycemia in normal rats by 50%. However, neither of the new glucagon antagonists lowered the plasma glucose levels of diabetic animals. The data would suggest these new glucagon-receptor antagonists may have two actions: (a) in normal rats they can act as standard glucagon-receptor inhibitors of glucagon-mediated glycogenolysis; (b) in diabetic rats, however, because of the low levels of glycogen in the liver, the antagonists apparently have little or no antagonist effect or enhancement on glucagon-mediated glucose production.
CT Medical Descriptors:
*diabetes mellitus
*dose response
*drug antagonism
*drug comparison
*drug receptor binding
*drug screening
*drug synthesis
*glucagon antagonist
*glucose blood level
rat
endocrine system
pharmacokinetics
nonhuman
etiology
blood and hemopoietic system
normal value
therapy
liver
animal experiment
animal cell
animal model
Drug Descriptors:
*adenylate cyclase
*cyclic amp
*glucagon derivative
***glucagon receptor**
streptozocin
*glucagon[3 aspartic acid 4 dextro phenylalanine 5 serine 17,18 lysine 21 glutamic acid]
*glucagon[4 dextro phenylalanine 5 tyrosine 10 (3,5 diiodotyrosine) 12 arginine 17,18 lysine 21 glutamic acid]
glucagon
glucagon i 125
new drug
radioisotope
unclassified drug
RN (adenylate cyclase) 9012-42-4; (cyclic amp) 60-92-4; (streptozocin) 18883-66-4; (glucagon) 11140-85-5, 62340-29-8, 9007-92-5

L93 ANSWER 15 OF 15 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN
AN 87179086 EMBASE
DN 1987179086

TI Interactions of beta adrenergic antagonists with isolated rat alveolar type II pneumocytes. II. Receptor-independent accumulation of beta adrenergic antagonists and other cationic **amphiphilic** drugs in lamellar bodies.
AU Fabisiak J.P.; Vesell E.S.; Rannels D.E.
CS Department of Pharmacology, College of Medicine, The Pennsylvania State University, The Milton S. Hershey Medical Center, Hershey, PA 17033, United States
SO Journal of Pharmacology and Experimental Therapeutics, (1987) 241/2 (728-735).
CODEN: JPETAB
CY United States
DT Journal
FS 037 Drug Literature Index
030 Pharmacology
LA English
CT Medical Descriptors:
*drug accumulation
*drug binding
*drug efficacy
*drug interaction
*lamellar body
*lymphoma cell
cell culture
lung alveolus cell
rat
priority journal
pharmacokinetics
respiratory system
in vitro study
nonhuman
animal cell
Drug Descriptors:
***beta adrenergic receptor**
*beta adrenergic receptor blocking agent
*(9 aminoacridinyl)propranolol
*chloroquine
*chlorpromazine
*cyanopindolol i 125
*indometacin
*iodopindolol i 125
*phentolamine
*phenytoin
*quinidine
*thiopental
radioisotope
unclassified drug
RN ((9 aminoacridinyl)propranolol) 60566-40-7; (chloroquine) 132-73-0, 3545-67-3, 50-63-5, 54-05-7; (chlorpromazine) 50-53-3, 69-09-0; (cyanopindolol i 125) 81447-77-0; (indometacin) 53-86-1, 74252-25-8, 7681-54-1; (iodopindolol i 125) 76875-01-9; (phentolamine) 50-60-2, 73-05-2; (phenytoin) 57-41-0, 630-93-3; (quinidine) 56-54-2; (thiopental) 71-73-8, 76-75-5
CO Polyscience (United States); Sigma (United States)

=> d all l98 tot

L98 ANSWER 1 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **1998275834** EMBASE
TI A system for the brain-enhanced delivery of estradiol: An assessment of its potential for the treatment of Alzheimer's disease and stroke.
AU Simpkins J.W.; Rabbani O.; Shi J.; Panickar K.S.; Green P.S.; Day A.L.
CS Dr. J.W. Simpkins, College of Pharmacy, University of Florida, Gainesville, FL 32610, United States
SO Pharmazie, (1998) 53/8 (505-511).
Refs: 88
ISSN: 0031-7144 CODEN: PHARAT
CY Germany
DT Journal; General Review
FS 008 Neurology and Neurosurgery
027 Biophysics, Bioengineering and Medical Instrumentation
030 Pharmacology
037 Drug Literature Index
LA English

CT Medical Descriptors:
*alzheimer disease
*stroke
*brain
*drug delivery system
cholinergic nerve cell
lipophilicity
blood brain barrier
hydrophilicity
lipid solubility
hydrolysis
oxidation reduction reaction
enzyme activity
neuroprotection
membrane depolarization
calcium homeostasis
human
nonhuman
review
Drug Descriptors:
*estradiol: AN, drug analysis
*estradiol: PK, pharmacokinetics
*estradiol: PD, pharmacology
*dihydropyridine
*pyridinium derivative
*3 hydroxy 17beta [[(1 methyl 1,4 dihydropyridine 3 yl)carbonyl]oxy]estra 1,3,5 (10) triene: AN, drug analysis
*1 methyl 3 [[(3 hydroxyestra 1,3,5 (10) triene 17beta yl)oxy]carbonyl]pyridinium iodide: AN, drug analysis
thromboxane: EC, endogenous compound
lipid: EC, endogenous compound
glucose: EC, endogenous compound
oxygen: EC, endogenous compound
excitatory amino acid: TO, drug toxicity
choline acetyltransferase: EC, endogenous compound
choline: EC, endogenous compound
calcium: EC, endogenous compound
cyclic amp responsive element binding protein: EC, endogenous compound
messenger rna: EC, endogenous compound
neurotrophin receptor: EC, endogenous compound
neurotrophin: EC, endogenous compound
mitogen activated protein kinase: EC, endogenous compound
nerve growth factor: EC, endogenous compound
amyloid beta protein: TO, drug toxicity
glutamic acid: TO, drug toxicity
buthionine sulfoximine: TO, drug toxicity
hydrogen peroxide: TO, drug toxicity
glucose transporter: EC, endogenous compound
diethylstilbestrol
neurotransmitter: EC, endogenous compound
unclassified drug
RN (estradiol) 50-28-2; (dihydropyridine) 27790-75-6; (thromboxane) 66719-58-2; (lipid) 66455-18-3; (glucose) 50-99-7, 84778-64-3; (oxygen) 7782-44-7; (choline acetyltransferase) 9012-78-6; (choline) 123-41-1, 13232-47-8, 1927-06-6, 4858-96-2, 62-49-7, 67-48-1; (calcium) 7440-70-2; (cyclic amp responsive element binding protein) 130428-87-4, 130939-96-7; (mitogen activated protein kinase) 142243-02-5; (nerve growth factor) 9061-61-4; (amyloid beta protein) 109770-29-8; (glutamic acid) 11070-68-1, 138-15-8, 56-86-0, 6899-05-4; (buthionine sulfoximine) 5072-26-4; (hydrogen peroxide) 7722-84-1; (diethylstilbestrol) 30498-85-2, 56-53-1

L98 ANSWER 2 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
AN **97275017** EMBASE
DN 1997275017
TI Use of conformationally restricted benzamidines as arginine surrogates in the design of platelet GPIIb-IIIa receptor antagonists.
AU Sall D.J.; Arfsten A.E.; Bastian J.A.; Denney M.L.; Harms C.S.; McCowan J.R.; Morin J.M. Jr.; Rose J.W.; Scarborough R.M.; Smyth M.S.; Um S.L.; Utterback B.G.; Vasileff R.T.; Wikel J.H.; Wyss V.L.; Jakubowski J.A.
CS D.J. Sall, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN 46285, United States
SO Journal of Medicinal Chemistry, (1997) 40/18 (2843-2857).
Refs: 37
ISSN: 0022-2623 CODEN: JMCMAR
CY United States

DT Journal; Article
FS 025 Hematology
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The use of 5,6-bicyclic amidines as arginine surrogates in the design of a novel class of potent platelet glycoprotein IIb-IIIa receptor (GPIIb-IIIa) antagonists is described. The additional conformational restriction offered by the bicyclic nucleus results in 20-400-fold increases in potency compared to the freely flexible, acyclic benzamidine counterpart. The design, synthesis, structure-activity relationships (SAR), and in vitro activity of this novel class of GPIIb-IIIa antagonists are presented.
CT Medical Descriptors:
*drug conformation
*drug design
*thrombocyte aggregation inhibition
article
drug potency
drug receptor binding
drug synthesis
enzyme linked immunosorbent assay
hydrogen bond
hydrophilicity
lipophilicity
structure activity relation
thrombocyte rich plasma
Drug Descriptors:
*arginine derivative
*benzamidine derivative: AN, drug analysis
*benzamidine derivative: PD, pharmacology
*benzamidine derivative: DV, drug development
*bicyclo compound
*fibrinogen receptor antagonist: PD, pharmacology
*fibrinogen receptor antagonist: DV, drug development
*fibrinogen receptor antagonist: AN, drug analysis
4 nitrophenyl phosphate
adenosine diphosphate
alkaline phosphatase
arginylglycylaspartic acid
avidin
benzofuran derivative
bovine serum albumin
fibrinogen
human serum albumin
vitronectin receptor
RN (4 nitrophenyl phosphate) 330-13-2; (adenosine diphosphate) 20398-34-9, 58-64-0; (alkaline phosphatase) 9001-78-9; (arginylglycylaspartic acid) 99896-85-2; (fibrinogen) 9001-32-5; (human serum albumin) 9048-49-1
CO Sigma (United States); Biorad (United States); Aldrich (United States)

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